



ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΘΡΟΜΒΩΣΗ ΚΑΙ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ



Μεταπτυχιακή Διπλωματική Εργασία

"ΣΥΝΔΡΟΜΟ ΥΠΕΡΔΙΕΓΕΡΣΗΣ ΩΟΘΗΚΩΝ ΚΑΙ ΦΛΕΒΙΚΕΣ ΘΡΟΜΒΩΣΕΙΣ"

ΥΠΟ

ΡΕΝΤΖΟΥ ΑΡΙΣΤΕΑΣ ΜΑΡΙΑΣ

Ειδικευόμενη Αναισθησιολογίας

Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση του
Διπλώματος Μεταπτυχιακών Σπουδών
«Θρόμβωση και Αντιθρομβωτική Αγωγή»

Λάρισα, 2025

Επιβλέπων:

Λευκού Ελευθερία, Επίκουρη Καθηγήτρια Ιατρικής Μεταγγίσεων, Τμήμα Ιατρικής,
Πανεπιστήμιο Θεσσαλίας

Τριμελής Εξεταστική Επιτροπή:

1. Λευκού Ελευθερία, Επίκουρη Καθηγήτρια Ιατρικής Μεταγγίσεων, Τμήμα Ιατρικής,
Πανεπιστήμιο Θεσσαλίας - *(Επιβλέπων)*
2. Τσιάρα Σταυρούλα, Καθηγήτρια Παθολογίας, Τμήμα Ιατρικής, Πανεπιστήμιο
Ιωαννίνων
3. Ρούσας Νικόλαος, Επίκουρος Καθηγητής Αγγειοχειρουργικής, Τμήμα Ιατρικής,
Δημοκρίτειο Πανεπιστήμιο Θράκης



FACULTY OF MEDICINE
SCHOOL OF HEALTH SCIENCES
UNIVERSITY OF THESSALY

MSc COURSE
THROMBOSIS AND ANTITHROMBOTIC TREATMENT



Master of Science Thesis

"OVARIAN HYPERSTIMULATION SYNDROME AND VENOUS THROMBOSIS"

by

RENTZOU ARISTEA MARIA

Resident in Anesthesiology

Submitted to fulfil part of the
requirements for the acquisition of the
Diploma of MSc Studies in
"Thrombosis and Antithrombotic Treatment"

Larissa, 2025

Supervisor:

Lefkou Eleftheria, Assistant Professor of Transfusion Medicine, Department of Medicine, University of Thessaly

Examination Committee:

1. Lefkou Eleftheria, Assistant Professor of Transfusion Medicine, Department of Medicine, University of Thessaly - (*Supervisor*)
2. Tsiara Stavroula, Professor of Internal Medicine, Department of Medicine, University of Ioannina
3. Rousas Nikolaos, Assistant Professor of Vascular Surgery, Department of Medicine, Democritus University of Thrace

Abstract:

This thesis explores the complex relationship between Ovarian Hyperstimulation Syndrome (OHSS) and venous thrombosis. It begins with a detailed analysis of OHSS, including its clinical presentation, pathophysiology, prevalence, and underlying mechanisms. Particular focus is placed on the prothrombotic state induced by OHSS, examining how vascular permeability, hemoconcentration, and hormonal factors contribute to thrombus formation. A comprehensive review of case reports involving venous thrombosis in OHSS patients was conducted, highlighting patterns in clinical presentation, timing, and outcomes. The data analysis provides insights into risk factors and the anatomical sites most commonly affected. Furthermore, the thesis delves into the proposed mechanisms linking OHSS to thrombosis and evaluates current approaches to treatment and prevention. Recommendations for early recognition, risk stratification, and management are discussed to reduce morbidity and improve outcomes. This work underscores the need for heightened awareness of thrombotic risks in women undergoing assisted reproductive treatments.

Key – Words:

Assisted Reproductive Technology, ART, OHSS, Ovarian Hyperstimulation Syndrome, Thromboembolism, Thrombosis Mechanisms, Venous Thrombosis

Περίληψη:

Η παρούσα διπλωματική εργασία διερευνά τη σύνθετη σχέση μεταξύ του Συνδρόμου Υπερδιέγερσης των Ωοθηκών (OHSS) και της φλεβικής θρόμβωσης. Ξεκινά με λεπτομερή ανάλυση του OHSS, περιλαμβάνοντας την κλινική του εικόνα, την παθοφυσιολογία, την επιδημιολογία και τους υποκείμενους μηχανισμούς. Ιδιαίτερη έμφαση δίνεται στην προθρομβωτική κατάσταση που προκαλείται από το OHSS, με ανάλυση του ρόλου της αγγειακής διαπερατότητας, της αιμοσυμπύκνωσης και των ορμονικών παραγόντων στη δημιουργία θρόμβων. Πραγματοποιήθηκε ανασκόπηση περιστατικών φλεβικής θρόμβωσης σε ασθενείς με OHSS, με στόχο την ανάδειξη προτύπων στην κλινική παρουσίαση, τον χρόνο εμφάνισης και την έκβαση. Η ανάλυση των δεδομένων προσφέρει πληροφορίες για τους παράγοντες κινδύνου και τις συχνότερα προσβεβλημένες ανατομικές περιοχές. Επιπλέον, η εργασία εξετάζει τους προτεινόμενους μηχανισμούς που συνδέουν το OHSS με τη θρόμβωση, καθώς και τις τρέχουσες στρατηγικές πρόληψης και θεραπείας. Τέλος, υπογραμμίζεται η ανάγκη για έγκαιρη αναγνώριση, εκτίμηση κινδύνου και σωστή διαχείριση, ιδιαίτερα σε γυναίκες που υποβάλλονται σε υποβοηθούμενη αναπαραγωγή.

Λέξεις – Κλειδιά:

Τεχνικές Υποβοηθούμενης Αναπαραγωγής, Σύνδρομο Υπερδιέγερσης Ωοθηκών, Θρομβοεμβολική Νόσος, Μηχανισμοί Θρόμβωσης, Φλεβική Θρόμβωση

Ευρετήριο Ακρωνύμιων

ADH: Antidiuretic Hormone	ISTH: International Society on Thrombosis and Haemostasis
AFC: Antral Follicle Count	iv: Intravenous
AKI: Acute Kidney Injury	IJV: Internal Jugular Vein
AMH: Anti-Müllerian Hormone	LH: Luteinizing Hormone
aPTT: Activated Partial Thromboplastin Time	LHR: LH Receptor
ART: Assisted Reproductive Technology	LMWH: Low-Molecular-Weight Heparin
ASRM: American Society for Reproductive Medicine	NA: Not Available
AT III: Antithrombin III	NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
BUN: Blood Urea Nitrogen	OAC: Oral Anticoagulant
COS: Controlled Ovarian Stimulation	OHSS: Ovarian Hyperstimulation Syndrome
CRP: C-Reactive Protein	OI: Ovulation Induction
CVT: Cerebral Venous Thrombosis	OS: Ovarian Stimulation
DOACs: Direct Oral Anticoagulants	PCOS: Polycystic Ovary Syndrome
DVT: Deep Vein Thrombosis	PE: Pulmonary Embolism
EJV: External Jugular Vein	PRA: Plasma Renin Activity
ESR: Erythrocyte Sedimentation Rate	PT: Prothrombin Time
ET: Embryo Transfer	RA: Right Atrium
FDP: Fibrin Degradation Products	RAAS: Renin-Angiotensin-Aldosterone System
FET: Frozen Embryo Transfer	RV: Right Ventricle
FVLM: Factor V Leiden Mutation	TnI: Troponin I
FSH: Follicle Stimulating Hormone	VEGF: Vascular Endothelial Growth Factor
FSHR: FSH Receptor	VKA: Vitamin K Antagonists
GnRH: Gonadotropin-Releasing Hormone	VT: Venous Throbosis
hCG: Human Chorionic Gonadotropin	VTE: Venous Thromboembolism
HS: Hormonal Stimulation	
ICOS: Individualized Controlled Ovarian Stimulation	
ICU: Intensive Care Unit	

Contents

General Section

Introduction _____	9
Statistics and Prevalence of OHSS and Thrombosis _____	11
Populations at Increased Risk and Risk Factors for Developing OHSS ____	12
Classification of OHSS _____	15
Clinical Presentations of OHSS _____	19
Pathophysiology of OHSS _____	24

Specific Section

Purpose of this Thesis _____	31
Methodology _____	31
Results _____	35
Discussion _____	40
Thrombosis Mechanism in OHSS _____	41
Therapy of OHSS and Venous Thrombosis _____	45
Management of Venous Thrombosis in OHSS _____	48
Prevention of OHSS and Venous Thrombosis _____	51
Prevention of Venous Thrombosis (VT) in ART and OHSS _____	53
Conclusion _____	57
References _____	59

Introduction

Ovarian Hyperstimulation Syndrome (OHSS) is a rare but significant iatrogenic complication associated with controlled ovarian stimulation (COS) in assisted reproductive technologies (ART). Despite advances in ART protocols, OHSS remains a leading cause of morbidity in fertility treatments, affecting 0.1–2% of ART cycles globally. The condition arises from an exaggerated ovarian response to gonadotropin stimulation, leading to ovarian enlargement and increased vascular permeability. These changes result in fluid shifts from the vascular compartment to third spaces, such as the abdominal cavity, pleura, or pericardium.

Spontaneous OHSS is a rare form of the syndrome that occurs without ovarian stimulation and is typically associated with elevated endogenous hCG levels. It has been observed in conditions such as gestational trophoblastic disease, multiple gestation pregnancies, and hypothyroidism. However, this subcategory falls outside the scope of this thesis and will not be addressed further.

OHSS is defined as a clinical syndrome that occurs as a result of excessive ovarian stimulation, typically in the context of fertility treatments. It is marked by a spectrum of symptoms and signs, ranging from mild discomfort to severe systemic complications. Central to its definition is the role of gonadotropins, which trigger an abnormal ovarian response and an increase in vascular endothelial growth factor (VEGF) activity. This cascade leads to increased capillary permeability and the hallmark fluid imbalances observed in this condition. OHSS is a condition unique to assisted reproduction, and its definition encompasses both its etiology and its clinical impact.

Clinically, OHSS manifests on a spectrum from mild discomfort, including bloating and nausea, to severe complications such as ascites, pleural effusion, oliguria, hemoconcentration, and thromboembolic events. The severe form of OHSS can be life-threatening, with multiorgan involvement and a need for intensive medical care.

The overall incidence of OHSS has significantly declined in recent years due to the implementation of preventive strategies, including the use of gonadotropin-

releasing hormone (GnRH) agonists as triggers for oocyte maturation and the adoption of “freeze-all” protocols, which allow the deferral of embryo transfer to later cycles. Despite these advances, mild to moderate forms of OHSS still occur in 20–33% of stimulated ART cycles, underscoring its frequent nature among women undergoing ovarian stimulation. Severe OHSS, characterized by substantial morbidity, affects approximately 0.1–2% of ART cycles. This prevalence varies based on stimulation protocols and population characteristics.

Thromboembolic events are among the most severe complications of OHSS, occurring in approximately 0.7–1.7% of cases with moderate to severe manifestations. These events predominantly affect the venous system, with deep vein thrombosis (DVT) and pulmonary embolism (PE) being the most commonly reported complications. Demographically, younger women undergoing ART, particularly those with polycystic ovary syndrome (PCOS) or a history of thrombophilia, are at a higher risk. The incidence is also influenced by the degree of hemoconcentration and immobilization during the course of OHSS. Regional studies have highlighted variability in the prevalence of thrombosis, linked to differences in clinical management practices and patient characteristics.

Although the adoption of personalized ovarian stimulation protocols has contributed to a reduction in severe cases, the risk of OHSS persists, emphasizing the need for ongoing research and refinement of ART practices.

The following chapters will provide an in-depth exploration of the mechanisms linking ovarian hyperstimulation syndrome to venous thrombosis, examine its clinical implications, and discuss preventive strategies within the context of assisted reproductive technologies. (1-3)

Statistics and Prevalence of OHSS and Thrombosis

The incidence of OHSS varies depending on the severity of the condition and the protocols used in ART. Mild OHSS is relatively common, occurring in approximately 20–33% of ovarian stimulation cycles. Moderate to severe OHSS is much less frequent, with reported incidence rates between 0.6% and 5%. Severe OHSS, which is characterized by major fluid shifts and organ dysfunction, is rare, affecting 0.1% to 2% of IVF cycles. Advances in ART, particularly modifications to ovarian stimulation protocols, such as the use of GnRH agonists, have contributed to a decline in severe OHSS cases in recent years.

Thrombosis, including both venous and arterial events, is a rare but serious complication of severe OHSS. Thrombotic events in OHSS are more commonly venous, but arterial thrombosis is also a significant concern. Thrombosis in this context typically occurs shortly after oocyte retrieval, during the period of greatest risk when OHSS symptoms are at their peak.

Venous thromboembolism (VTE) is a well-known complication of OHSS. The incidence of VTE in severe OHSS cases ranges from 0.7% to 10%, with the risk being highest in the first two weeks following ovulation induction. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the most commonly observed venous thrombotic events in OHSS patients.

Arterial thrombosis, while less common than venous thrombosis, is an important and potentially fatal complication of severe OHSS. The reported incidence of arterial thrombosis in OHSS ranges from 0.2% to 1%. These events often present as ischemic stroke, myocardial infarction, or peripheral limb ischemia. (4,5)

Populations at Increased Risk and Risk Factors for Developing OHSS

OHSS is a multifactorial condition influenced by a variety of clinical, demographic, and treatment-related factors. Pregnant women undergoing assisted reproductive technology (ART) constitute a vulnerable population, as pregnancy itself induces a hypercoagulable state through increased levels of coagulation factors (e.g., fibrinogen, factor VIII) and decreased fibrinolytic activity. Studies estimate the risk of VTE in pregnancy increases by 4–5 times compared to non-pregnant women. This risk may be even higher in the context of severe OHSS. Similarly, women with polycystic ovary syndrome (PCOS) are at increased risk due to their tendency for exaggerated ovarian responses to stimulation protocols. Women with PCOS undergoing ART can have up to a 50% higher risk of developing OHSS compared to those without the condition. Other significant risk factors include high baseline estradiol levels, elevated antral follicle counts, and a history of severe OHSS in prior ART cycles, all of which increase the likelihood of thromboembolic events.

Additionally, several individual characteristics influence the risk of developing OHSS. Younger women, particularly those under 35, are at greater risk of developing severe OHSS, likely due to a more robust ovarian response to stimulation protocols. Studies show that women aged 30 or younger have up to a 40% increased risk of severe OHSS compared to older women. Women with a lower body mass index (BMI) are also more susceptible, with studies showing that those with a BMI under 25 kg/m² may be more likely to experience severe OHSS. Conversely, overweight and obese women (BMI ≥ 30) may have a lower ovarian response to stimulation but still face increased risks of complications during ART. Furthermore, a history of previous pregnancies, especially multiple pregnancies, can increase the likelihood of developing OHSS, likely due to hormonal sensitivity and ovarian response patterns. Women with a history of hyperstimulated ovaries in prior ART cycles are also at higher risk.

A history of OHSS in previous cycles serves as a strong predictor for recurrence, emphasizing the need for careful monitoring and tailored protocols in subsequent ART attempts. It is estimated that women who experienced severe OHSS in prior ART cycles are 3-4 times more likely to develop it again.

The use of human chorionic gonadotropin (hCG) as a trigger for ovulation or for luteal phase support significantly exacerbates the risk of OHSS, primarily due to its prolonged luteotropic effects, which sustain ovarian hyperstimulation. hCG acts similarly to luteinizing hormone (LH) and can increase vascular permeability, contributing to the fluid shift and ascites characteristic of OHSS.

Other contributing factors include the type and dosage of ovarian stimulation protocols used, as high-dose regimens or certain gonadotropin preparations may disproportionately increase the risk of OHSS. In particular, the use of recombinant FSH (Follicle Stimulating Hormone) has been associated with higher rates of OHSS compared to traditional urinary-derived FSH preparations. The timing and method of hCG administration are also critical, with some regimens causing more pronounced ovarian stimulation than others. For example, the use of long-acting hCG formulations has been associated with an increased incidence of OHSS due to prolonged ovarian stimulation and sustained elevated hormone levels.

Additionally, women undergoing fresh embryo transfers are more likely to develop OHSS compared to those utilizing freeze-all strategies, as the hormonal milieu during fresh transfers often exacerbates the condition. A fresh embryo transfer results in the additional hormonal stimulation needed for implantation, further aggravating the already fragile hormonal balance in women at risk for OHSS. Women using freeze-all strategies, on the other hand, can reduce the risk of developing OHSS by delaying embryo transfer until the ovaries have time to recover and hormone levels stabilize.

Regarding OHSS vascular complications and more specifically thrombosis, certain populations are disproportionately predisposed to developing them. Women with thrombophilia, either inherited or acquired, represent a high-risk group due to their underlying predisposition to clot formation. Inherited conditions such as Factor V Leiden mutation, present in approximately 4–5% of the general population, can increase the risk of venous thromboembolism (VTE) by about 3-fold in heterozygotes and significantly more in homozygotes. Similarly, the prothrombin gene mutation (G20210A) is associated with a 2–3-fold higher risk of thrombosis. Acquired conditions like antiphospholipid

syndrome can further amplify thrombosis risk. In the hypercoagulable environment created by OHSS, these risks are further compounded.

Collectively, these risk factors underscore the importance of individualized treatment approaches and vigilant monitoring in high-risk populations. Customizing ovarian stimulation protocols based on a woman's specific risk factors can significantly reduce the likelihood of severe OHSS and improve ART outcomes. (6-11)

Classification of OHSS

OHSS results in a range of symptoms, from mild discomfort to severe complications, depending mostly on the degree of ovarian enlargement and systemic involvement.

The most widely recognized system for staging ovarian hyperstimulation syndrome (OHSS) is the classification proposed by Golan et al. This framework integrates clinical manifestations, ultrasonographic features, and laboratory parameters to stratify OHSS severity into three levels and five grades (Table 1). Reports indicate that the incidence of OHSS in COH patients may reach up to 33% when classified using this system.

OHSS classification.

Grade	OHSS Stage		
	Mild	Moderate	Severe
1	Abdominal distension/discomfort		
2	Features of grade 1 plus nausea, vomiting, and/or diarrhea Ovaries enlarged to 5–12 cm		
3		Features of mild OHSS plus ultrasonographic evidence of ascites	
4			Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax or difficulty in breathing
5			All of the above plus change in blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function

(Table 1) Whelan JG 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. *Fertil Steril*. 2000 May;73(5):883-96. doi: 10.1016/s0015-0282(00)00491-x. PMID: 10785212.

A noted limitation of the Golan classification is its inability to differentiate patients within the "severe" category who are at imminent risk of life-threatening complications. Whelan et al. suggest that all cases categorized as severe by this system should be considered potentially critical, warranting close monitoring and inpatient management.

According to the guidelines of the American Society for Reproductive Medicine (ASRM), OHSS is classified into three categories—mild, moderate, severe and critical—based on clinical and laboratory features (Table 2). Although the most recent ASRM guidelines do not incorporate ovarian size as a criterion for classifying OHSS severity, earlier publications have utilized ovarian dimensions

as an indicator of disease severity, therefore we will discuss its significance in this context.

Classification of ovarian hyperstimulation syndrome (OHSS) symptoms.		
OHSS stage	Clinical features	Laboratory features
Mild	Abdominal distension/discomfort Mild nausea/vomiting Mild dyspnea Diarrhea Enlarged ovaries	No important alterations
Moderate	Mild features + Ultrasonographic evidence of ascites	Hemoconcentration (Hct >41%) Elevated WBC (>15,000 mL)
Severe	Mild and moderate features + Clinical evidence of ascites Hydrothorax Severe dyspnea Oliguria/anuria Intractable nausea/vomiting	Severe hemoconcentration (Hct >45%) WBC >25,000 mL CrCl <50 mL/min Cr >1.6 mg/dL Na+ <135 mEq/L K+ >5 mEq/L Elevated liver enzymes
Critical	Low blood/central venous pressure Pleural effusion Rapid weight gain (>1 kg in 24 h) Syncope Severe abdominal pain Venous thrombosis Anuria/acute renal failure Arrhythmia Thromboembolism Pericardial effusion Massive hydrothorax Arterial thrombosis Adult respiratory distress syndrome Sepsis	Worsening of findings

Cr = creatinine; CrCl= creatinine clearance; Hct = hematocrit; K+ = potassium; Na+ = sodium; WBC = white blood cell.

Adapted from: Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. *Fertil Steril* 1992;58:249-61.

Terms of use: Fiedler K, Ezcurra D. Predicting and preventing ovarian hyperstimulation syndrome (OHSS): the need for individualized not standardized treatment. *Reproductive Biology and Endocrinology* 2012;10:32. © 2012 Fiedler and Ezcurra; licensee BioMed Central Ltd. This work is licensed under a Creative Commons Attribution 2.0 Generic License: <http://creativecommons.org/licenses/by/2.0>. It is attributed to Klaus Fiedler and Diego Ezcurra, and the original version can be found at <http://rbej.biomedcentral.com/articles/10.1186/1477-7827-10-32#CR9>.

Hayes. OHSS. *Fertil Steril* 2024.

Table 2. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Prevention of moderate and severe ovarian hyperstimulation syndrome: a guideline. *Fertil Steril*. 2024 Feb;121(2):230-245. doi: 10.1016/j.fertnstert.2023.11.013. Epub 2023 Dec 13. Erratum in: *Fertil Steril*. 2024 Dec 1:S0015-0282(24)02306-9. doi: 10.1016/j.fertnstert.2024.10.012. PMID: 38099867.

In mild OHSS, ovarian enlargement is generally modest, with ovaries measuring between 5 to 8 cm in diameter. This enlargement is due to multiple small cysts within the ovaries, characteristic of mild cases of OHSS. There is minimal or no fluid accumulation in the abdominal cavity, and the ovaries remain mobile and non-tender upon palpation. The primary symptoms of mild OHSS are abdominal discomfort, often experienced as bloating, fullness, or a sense of pressure in the lower abdomen. While the discomfort can be annoying, it is usually not severe enough to affect daily activities. Some patients may also experience mild nausea, which is often temporary, and in rarer cases, vomiting. Abdominal pain in mild OHSS is generally tolerable, and symptoms usually resolve within 3-5 days. Laboratory findings in these cases typically show slight hemoconcentration, indicated by mildly elevated hematocrit and hemoglobin levels due to fluid shifts from the intravascular space. However, electrolyte

levels usually remain normal, and renal function is unaffected. Management for mild OHSS is mostly conservative, involving hydration and symptomatic relief, often requiring no more than outpatient care.

Moderate OHSS is marked by more noticeable ovarian enlargement, with ovaries often measuring between 8 and 12 cm. Ascites is present, which may lead to increased abdominal girth and discomfort. This condition may also result in mild respiratory issues if the ascites extends into the diaphragm, but pleural effusion is not as common as in severe cases. The symptoms are more intense than in mild OHSS, and patients may experience significant abdominal distension, leading to a sensation of tightness in the abdomen, which can interfere with daily activities. Nausea and vomiting are more frequent and persistent in moderate cases, and some patients may also experience diarrhea. Reduced urine output, or oliguria, is another hallmark of moderate OHSS, indicating fluid shifts away from the vascular compartment. Laboratory tests reveal more pronounced hemoconcentration compared to mild OHSS, with elevated hematocrit and hemoglobin levels. Electrolyte disturbances, particularly hypokalemia, may also develop due to fluid imbalance, though renal function typically remains stable. Treatment for moderate OHSS involves close monitoring, hydration, and electrolyte management. In some cases, intravenous hydration or diuretics may be used to manage fluid buildup, and hospitalization may be required for further monitoring.

Severe OHSS represents the most extreme and potentially life-threatening form of the syndrome. Ovaries in severe OHSS are often significantly enlarged, measuring over 12 cm, and may contain large cysts. Massive fluid accumulation occurs not only in the abdominal cavity but also in the pleural and pericardial spaces, leading to pleural effusion and pericardial effusion. These fluid shifts can cause significant respiratory distress, resulting in shortness of breath and impaired cardiac function. Abdominal pain in severe OHSS is often severe and can be associated with ovarian torsion, a medical emergency that occurs when the enlarged ovaries twist, cutting off their blood supply. Patients with severe OHSS may experience significant nausea, vomiting, and diarrhea. In addition, hypotension can develop as a result of the significant fluid shifts and hemoconcentration, leading to decreased perfusion to vital organs. Renal

failure is another potential complication, often caused by hypovolemia, which reduces kidney perfusion and results in acute kidney injury (AKI). Electrolyte imbalances are common, including hyperkalemia and hyponatremia, and coagulation abnormalities, such as prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), may also occur, increasing the risk of thromboembolic events like deep vein thrombosis (DVT) or pulmonary embolism (PE).

Critical OHSS includes all severe features, with additional symptoms such as tense ascites and large hydrothorax. Laboratory findings often reveal a hematocrit greater than 55% and a white blood cell count exceeding 35,000/ μ L. Patients may experience anuria, elevated serum creatinine levels above 2.0 mg/dL, and creatinine clearance below 20 mL/min. Serious complications include thromboembolic events and acute respiratory distress syndrome (ARDS).

Additionally, based on the timing of its onset, ASRM classifies OHSS in early and late onset. Early-Onset OHSS typically occurs within 4–7 days following the administration of human chorionic gonadotropin (hCG). This form is generally related to the initial ovarian response to stimulation protocols and it is more common in patients with high ovarian reserve, such as those with polycystic ovary syndrome (PCOS) or high antral follicle counts. Late-Onset OHSS develops more than 9 days after the hCG trigger and tends to be more severe with a prolonged clinical course. This variant is often associated with rising endogenous hCG levels due to ongoing pregnancy and patients who conceive during the cycle are at a higher risk of developing this form. (12, 73)

Clinical Presentations of OHSS

Ovarian Hyperstimulation Syndrome (OHSS) presents with a wide range of symptoms that can vary in severity, depending on the degree of ovarian enlargement and the extent of systemic involvement. While some cases are mild and self-limiting, others can escalate to severe forms with life-threatening complications, with severity corresponding to the classification of OHSS.

One of the hallmark symptoms of OHSS, irrespective of its severity, is abdominal distension. As ovarian size increases, the ovaries become enlarged, often due to the formation of multiple cysts. In mild OHSS, the enlargement is modest, and the patient may experience a sensation of bloating or fullness in the lower abdomen. This can be bothersome but typically does not interfere significantly with daily activities. However, in moderate to severe cases, the distension can become much more pronounced, causing discomfort or even severe abdominal pain. The pain in OHSS is often described as a sense of pressure or heaviness in the abdomen, and it may worsen with increased ovarian size or the accumulation of fluid in the abdominal cavity. In more severe cases, the pain may become cramp-like or sharp, particularly if complications such as ovarian torsion occur. Ovarian torsion, where the enlarged ovaries twist and cut off their blood supply, is a serious emergency that can lead to intense pain and necessitates immediate intervention. Severe abdominal pain, especially when associated with nausea and vomiting, should raise suspicion for this complication. In addition to pain and distension, patients with moderate and severe OHSS may experience difficulty in moving comfortably due to the enlargement of the ovaries and the fluid accumulation. The abdomen may feel tight or rigid, leading to further discomfort. As the condition progresses, these symptoms can significantly impact a patient's ability to perform regular tasks, leading to increased concern for both physical and emotional well-being.

Gastrointestinal disturbances are common in OHSS, particularly in moderate and severe cases, due to the effect of fluid accumulation on the abdominal organs. Nausea is one of the most frequently reported symptoms in these patients and can range from mild to severe. It is often accompanied by vomiting, which can exacerbate fluid loss and dehydration. These symptoms may persist

for several days, and in more severe forms of the condition, they can become debilitating, causing significant distress and discomfort for the patient. In addition to nausea and vomiting, diarrhea may also be present, particularly in moderate cases of OHSS. The presence of diarrhea is thought to result from the abdominal distention and irritation of the gastrointestinal tract by the excess fluid in the abdominal cavity. This can further contribute to fluid imbalance, making management of the syndrome more complex. Although gastrointestinal symptoms are less severe in mild cases of OHSS, the presence of nausea or bloating can still affect the patient's overall quality of life. The gastrointestinal symptoms, particularly when accompanied by vomiting, can lead to a significant decrease in oral intake, resulting in even more electrolyte imbalances and fluid deficits. Thus, managing these symptoms promptly through hydration and electrolyte replacement is essential to prevent further complications, such as kidney injury or thromboembolic events.

As OHSS progresses to moderate or severe stages, fluid accumulation extends beyond the abdominal cavity, potentially involving the pleural and pericardial spaces. As a first consideration, when ascites becomes extensive, it can press on the diaphragm making it difficult for the lungs to expand fully. This results in symptoms of respiratory distress, including shortness of breath and difficulty breathing. This can be particularly distressing for individuals who are already dealing with abdominal discomfort and gastrointestinal symptoms. The severity of respiratory symptoms correlates with the amount of fluid accumulation and the extent of pleural effusion. Pleural effusion is particularly concerning in severe OHSS and can lead to significant respiratory compromise. In some cases, patients may experience hypoxia due to impaired lung function from fluid buildup. Additional possible signs and symptoms may be a sensation of tightness in the chest, increased work of breathing, and rapid shallow breaths. Severe cases may require oxygen therapy or more intensive management to stabilize the patient's condition.

Pericardial effusion is a less common but serious complication of severe OHSS, which may also contribute to respiratory symptoms and impaired cardiovascular function. This occurs due to the abnormal fluid shift associated

with OHSS, leading to fluid accumulation in the pericardial sac that can cause cardiac tamponade in rare instances.

The kidneys are often affected by the fluid shifts that occur in OHSS, particularly in moderate and severe forms of the syndrome. As fluid accumulates in the abdominal cavity and other spaces, the decreased circulating blood volume can lead to decreased renal perfusion, impairing kidney function and resulting in oliguria. Oliguria is often one of the first signs that kidney function is being compromised and may be seen in patients with moderate OHSS.

In more severe cases, fluid shifts can cause hypovolemia, which may lead to acute kidney injury and even anuria. The kidneys' inability to filter waste products efficiently can lead to an accumulation of toxins in the bloodstream, contributing to electrolyte imbalances such as elevated serum creatinine and blood urea nitrogen (BUN) levels. More serious abnormalities, such as hyperkalemia or hyponatremia, may also arise and have the potential to cause life-threatening complications. Severe renal dysfunction can complicate the clinical course of OHSS, necessitating close monitoring of renal function and, in some cases, renal replacement therapy, such as dialysis, to manage the patient's condition.

Systemic manifestations are often seen in severe OHSS due to the widespread impact of the condition on multiple organ systems. One of the most concerning systemic symptoms is hypotension, which occurs due to the significant fluid shifts from the intravascular space to the third space. As the blood volume decreases and hemoconcentration increases, there is less perfusion to vital organs, leading to a drop in blood pressure. Hypotension can worsen renal perfusion and exacerbate the risk of acute kidney injury, while also affecting cardiovascular stability. In some cases, shock can occur if the fluid shifts are severe enough to cause profound circulatory instability. Shock can be associated with multiple organ failure, requiring intensive care and immediate intervention.

Another significant systemic complication of OHSS is the increased risk of thromboembolic events, driven by hemoconcentration, hypercoagulability, and altered hemodynamics. While deep vein thrombosis (DVT) and pulmonary

embolism (PE) are well-recognized complications, the pattern of thrombosis in OHSS is notable for its tendency to involve atypical sites, reflecting the unique pathophysiology of the syndrome.

Clinical presentations vary depending on the site of thrombus formation. Lower extremity DVT typically manifests as unilateral leg swelling, pain, warmth, and erythema, whereas pulmonary embolism, a potentially fatal complication, presents with acute-onset chest pain, shortness of breath, hemoptysis, or hemodynamic instability. However, in OHSS, thrombosis frequently involves unusual locations, such as the internal jugular veins, subclavian veins, renal veins, and cerebral venous sinuses. Internal jugular vein thrombosis can present with neck swelling, pain, and occasionally systemic signs of infection, while cerebral venous thrombosis (CVT) may cause headache, seizures, visual disturbances, or altered mental status. Renal vein thrombosis, though rare, is associated with flank pain and hematuria and may lead to kidney dysfunction if untreated.

While DVT remains a significant site of thrombosis in OHSS, studies suggest that it is not always the most common. Upper extremity thrombosis, particularly involving the internal jugular or subclavian veins, may occur as frequently as, or even exceed, DVT in prevalence among patients with OHSS. Cerebral venous thrombosis, though rare, is another notable complication that requires vigilance due to its potentially catastrophic outcomes. Pulmonary embolism, which often results from migration of a thrombus from other venous sites, accounts for a substantial proportion of thromboembolic events and poses a significant risk of morbidity and mortality. Epidemiological studies indicate that the overall incidence of thromboembolic events in severe OHSS ranges from 0.7% to 10%. Among these, unusual sites of thrombosis comprise a significant proportion of cases, with internal jugular vein and subclavian vein thrombosis frequently reported. Pulmonary embolism is estimated to account for 10–15% of thrombotic events, while cerebral venous thrombosis remains rare, occurring in less than 1% of cases. These findings underscore the distinct thrombotic profile of OHSS, which differs from that seen in the general population. Given the diverse clinical spectrum of thrombosis in OHSS, early recognition and appropriate preventive strategies are paramount. Close monitoring for signs of

thrombosis, particularly in atypical locations, and prophylactic anticoagulation - typically with low molecular weight heparin- are often employed in high-risk patients to ensure timely diagnosis and intervention. (13-15)

Pathophysiology of OHSS

A deep understanding of the pathophysiology of ovarian hyperstimulation syndrome (OHSS) is vital for its prevention, early recognition, and effective management. As a potentially serious complication of assisted reproductive treatments, OHSS poses significant health risks if not carefully monitored. By exploring its underlying mechanisms—such as increased vascular permeability, fluid imbalances, and the influence of hormonal and inflammatory factors—clinicians can better identify high-risk patients, refine stimulation protocols, and implement targeted interventions to enhance patient safety and outcomes (Figure 1).

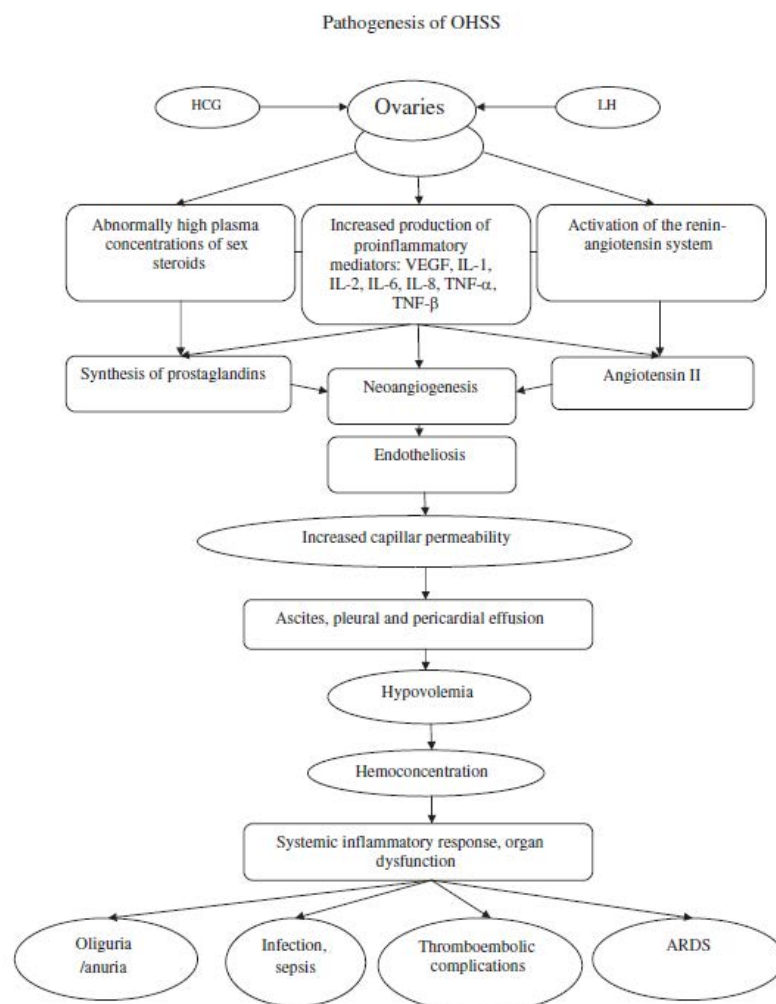


Figure 1. Petrenko AP, Castelo-Branco C, Marshalov DV, Salov IA, Shifman EM. Ovarian hyperstimulation syndrome. A new look at an old problem. *Gynecol Endocrinol*. 2019 Aug;35(8):651-656. doi: 10.1080/09513590.2019.1592153. Epub 2019 Apr 2. PMID: 30935259.

The development of OHSS is intricately linked to the administration of exogenous gonadotropins, primarily follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are used to stimulate the growth and maturation of multiple ovarian follicles in controlled ovarian hyperstimulation protocols. These gonadotropins are administered in high doses to override the natural inhibitory mechanisms that limit follicular recruitment. In individuals predisposed to OHSS, this exogenous stimulation leads to an exaggerated ovarian response, characterized by the development of numerous large follicles. The overstimulated ovaries release a variety of bioactive molecules, including cytokines and other growth factors, which exacerbate the local and systemic manifestations of OHSS. Additionally, the interplay between gonadotropins and ovarian stromal cells further amplifies the cascade of events. The excessive production of estradiol by granulosa cells within the follicles serves as an early marker of heightened ovarian activity. Estradiol levels can rise exponentially, reflecting the hyper-responsiveness of the ovaries.

The hormonal environment plays a critical role in the pathophysiology of OHSS, with human chorionic gonadotropin (hCG) and estradiol being two key players that drive the cascade of events leading to vascular hyperpermeability and fluid shifts. hCG is a hormone that mimics luteinizing hormone (LH) and is central to the development of OHSS. It is used exogenously to trigger ovulation in assisted reproductive technologies and can also be produced endogenously following successful fertilization. hCG acts as a luteotropic agent, stimulating granulosa cells to undergo luteinization and further promoting the production of various vasoactive substances, including vascular endothelial growth factor (VEGF), which is a major mediator of vascular permeability. The elevation of hCG levels during ovarian stimulation protocols directly leads to an increase in VEGF secretion, amplifying the vascular leakage that characterizes OHSS and thus, hCG indirectly upregulates significantly the vascular abnormalities seen in OHSS.

In addition to hCG, estradiol plays a synergistic role in the pathogenesis of OHSS. Estradiol is produced in large quantities by the developing ovarian follicles during stimulation, and its levels can rise exponentially in patients who

are prone to OHSS. Elevated estradiol levels enhance the sensitivity of ovarian cells to gonadotropins and contribute to the hyper-responsiveness of the ovaries. Furthermore, estradiol also stimulates the secretion of VEGF, further exacerbating the endothelial dysfunction and vascular permeability associated with the syndrome. Estradiol's influence extends beyond its direct effects on VEGF; it also modulates the production of other inflammatory mediators and cytokines, contributing to the systemic inflammatory response that enhances vascular leakage.

The combined effect of hCG and estradiol in promoting VEGF production and endothelial dysfunction underscores the hormonal basis for the development of OHSS. These hormones create a synergistic environment that drives excessive ovarian stimulation and alters vascular permeability, therefore understanding the roles of hCG and estradiol in OHSS is crucial for identifying potential future therapeutic targets and strategies.

Vascular Endothelial Growth Factor (VEGF) plays a pivotal role in the pathophysiology of OHSS by driving vascular hyperpermeability and fluid accumulation. VEGF is produced in response to the hormonal stimulation of granulosa and luteal cells, particularly under the influence of human chorionic gonadotropin (hCG). It acts by binding to VEGF receptors, notably VEGFR-2, on endothelial cells lining the vasculature. This interaction triggers a signaling cascade, with VEGFR-2 being the most critical receptor expressed on endothelial cells. This binding activates the receptor's intrinsic kinase activity, resulting in the phosphorylation of key tyrosine residues on the receptor's cytoplasmic domain. This phosphorylation event triggers downstream signaling cascades, most notably the phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) pathways. These pathways are crucial for regulating endothelial cell survival, proliferation, and permeability.

A key outcome of VEGFR-2 activation is the disruption of endothelial tight junctions, which are responsible for maintaining the integrity of the endothelial monolayer and preventing fluid leakage. VEGF-induced phosphorylation of junctional proteins such as VE-cadherin, claudins, and occludins weakens these tight junctions, destabilizing the endothelial barrier. As a result, plasma

proteins and fluid are able to extravasate into surrounding tissues and third spaces. This disruption of endothelial integrity is central to the increased vascular permeability and fluid depletion observed in OHSS. The transudation of fluid is driven by the imbalance between hydrostatic and oncotic pressures, compounded by the loss of plasma proteins from circulation. Hypoalbuminemia, resulting from this protein sequestration, further reduces the intravascular colloid osmotic pressure and perpetuates fluid extravasation.

In addition to disrupting tight junctions, VEGF signaling promotes angiogenesis, or the formation of new blood vessels. This process, which is essential for ovarian follicular development, contributes to the increased capillary density observed in the ovaries during OHSS. However, the newly formed blood vessels are often structurally immature and more prone to leakage, further exacerbating fluid extravasation and the associated complications.

VEGF-induced endothelial dysfunction is further amplified by the production of additional vasoactive substances, including nitric oxide (NO) and prostacyclin (PGI₂). These molecules play key roles in modulating endothelial cell behavior and enhancing vascular permeability. Nitric oxide (NO) is synthesized in endothelial cells through the activation of endothelial nitric oxide synthase (eNOS), in response to VEGF stimulation. NO acts as a potent vasodilator, relaxing smooth muscle cells and increasing blood flow. In the context of OHSS, NO not only promotes vasodilation but also increases endothelial cell permeability. It does so by modulating the actin cytoskeleton, which disrupts the organization of tight junctions and leads to the formation of endothelial gaps, further facilitating the leakage of fluid and plasma proteins into the extravascular spaces.

Similarly, prostacyclin (PGI₂), produced through the cyclooxygenase (COX) pathway in response to VEGF, contributes to increased vascular permeability by binding to its receptor, IP, on endothelial cells. This interaction activates intracellular signaling pathways that promote the opening of endothelial junctions, increasing the likelihood of fluid extravasation. Additionally, prostacyclin induces vasodilation, elevating capillary pressure and further enhancing fluid leakage into surrounding tissues.

The combined effects of VEGF, NO, and prostacyclin on endothelial cells create a synergistic cascade that significantly contributes to the vascular hyperpermeability seen in OHSS. By disrupting tight junctions, promoting angiogenesis, and modulating vascular tone, these mediators work together to amplify the fluid shifts and other systemic complications characteristic of the syndrome. Additionally, the hypovolemia caused by fluid shifts triggers compensatory mechanisms, including the activation of the renin-angiotensin-aldosterone system (RAAS) and the release of antidiuretic hormone (ADH). While these mechanisms aim to restore circulatory stability, they can exacerbate fluid retention and third-spacing, worsening the symptoms of OHSS. Reduced renal perfusion due to hypovolemia may also impair kidney function, leading to oliguria or acute kidney injury (AKI) in severe cases.

The pathophysiology of OHSS is not only driven by VEGF-induced vascular permeability but is also significantly influenced by a range of inflammatory mediators and cytokines. Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) are crucial in amplifying the effects of VEGF and further promoting endothelial dysfunction. These cytokines are released by various cell types, including granulosa cells in the ovaries, as well as immune cells that are recruited to the site of injury or inflammation. In response to VEGF signaling, IL-6 and TNF- α enhance endothelial cell activation and contribute to the disruption of tight junctions between endothelial cells, thereby increasing vascular permeability.

IL-6, a pleiotropic cytokine, has several roles in inflammation and immune regulation. It can activate the JAK/STAT signaling pathway, which leads to the expression of additional pro-inflammatory mediators that promote vascular leakage. Elevated levels of IL-6 have been associated with the severity of OHSS, as they contribute to the systemic inflammatory response and exacerbate the vascular dysfunction induced by VEGF. Similarly, TNF- α is a potent pro-inflammatory cytokine that can induce endothelial cell activation, further promoting the release of vasoactive substances, including additional cytokines, prostanoids, and nitric oxide. TNF- α also stimulates the expression of adhesion molecules on endothelial cells, facilitating the recruitment and activation of leukocytes. This immune cell activation amplifies the local

inflammatory response, creating a vicious cycle that perpetuates the endothelial dysfunction seen in OHSS.

In addition to IL-6 and TNF- α , other cytokines, including interleukin-1 β (IL-1 β) and interferon- γ (IFN- γ), can contribute to the inflammatory milieu in OHSS. These cytokines can further activate immune cells, recruit neutrophils, and upregulate the production of additional inflammatory mediators. The recruitment of leukocytes to the site of vascular injury exacerbates endothelial cell activation and permeability, amplifying the fluid leakage and systemic inflammatory response.

The interaction between VEGF and these inflammatory mediators highlights the complex, multifactorial nature of OHSS. VEGF not only drives the structural changes in endothelial cells but also enhances the production of pro-inflammatory cytokines, creating a feedback loop that exacerbates vascular permeability and tissue edema. This intricate interplay between VEGF and inflammatory mediators underscores the importance of addressing both vascular and immune pathways in the management of OHSS.

Genetic factors -while interacting with environmental factors- can also play an important role in the development and severity of OHSS, influencing an individual's susceptibility to the condition. Variations in genes related to ovarian function, gonadotropin receptor activity, and vascular endothelial growth factor (VEGF) signaling can predispose certain individuals to an exaggerated ovarian response, increasing the risk of developing OHSS.

One of the most significant genetic factors associated with OHSS is polymorphisms in the VEGF gene. Variations in the VEGF gene or its receptors can lead to increased sensitivity to VEGF signaling. Certain polymorphisms in the VEGFR-2 receptor gene have been linked to an enhanced response to VEGF, resulting in a greater propensity for vascular permeability and fluid leakage. Such genetic predispositions may contribute to the development of OHSS, especially in individuals undergoing assisted reproductive technologies where VEGF expression is already elevated.

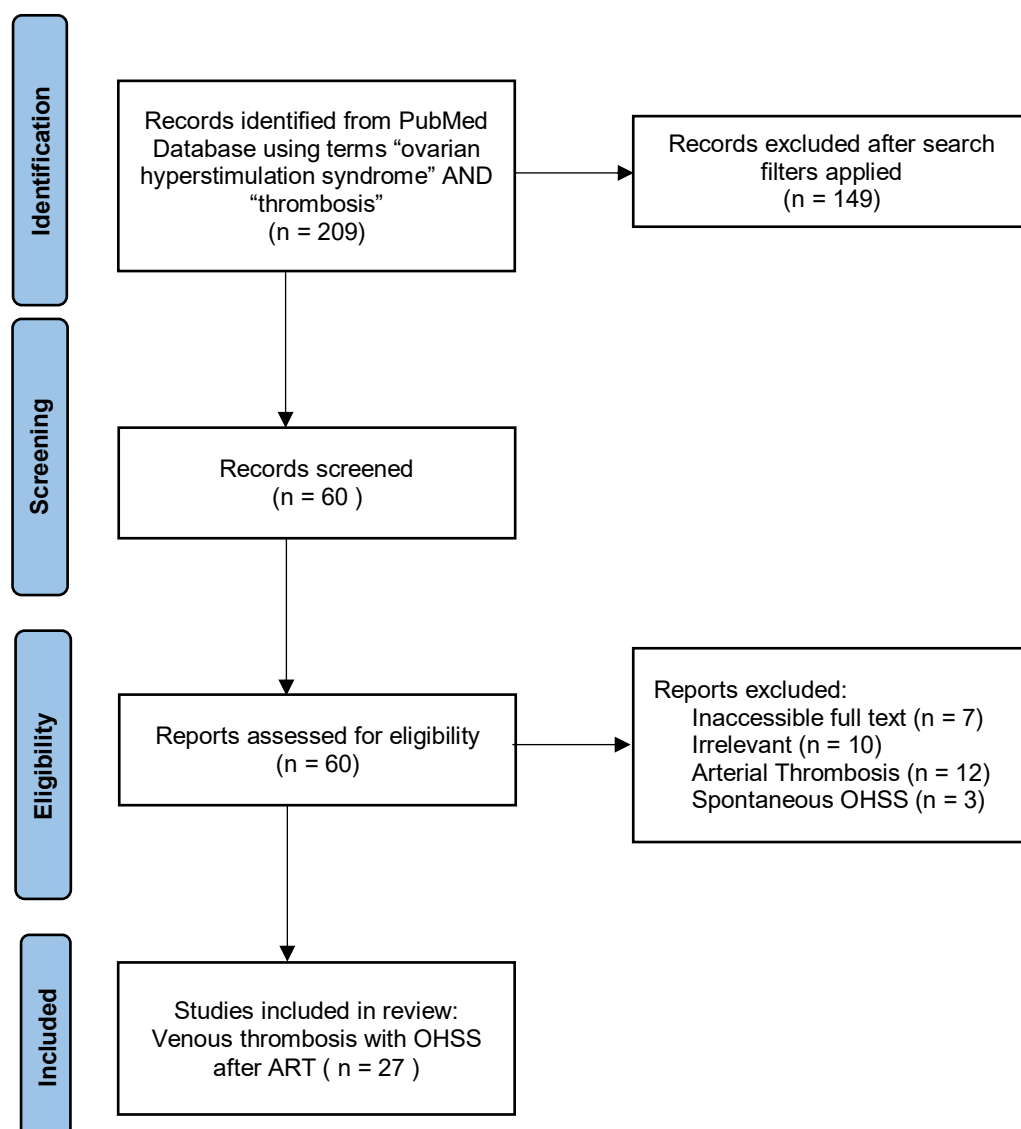
In addition to VEGF-related genetic variations, genetic differences in gonadotropin receptors may also increase susceptibility to OHSS. The FSH receptor (FSHR) gene and LH receptor (LHR) gene are crucial in regulating the ovarian response to exogenous gonadotropins. Polymorphisms in these genes can result in an altered receptor function, leading to an exaggerated ovarian response to stimulation. For example, individuals with certain polymorphisms in the FSH receptor gene may experience an increased number of follicular recruitments or greater follicular sensitivity to gonadotropins, which can predispose them to the development of OHSS when undergoing fertility treatments.

Moreover, genetic variations in the cytokine genes, particularly those involved in inflammatory pathways, may also influence the severity of OHSS. Variants in genes encoding for pro-inflammatory cytokines like IL-6 and TNF- α can lead to an enhanced inflammatory response, amplifying endothelial dysfunction and vascular permeability and predisposing individuals to more severe manifestations of OHSS. (16-27)

Purpose of this Thesis

The purpose of this research is to systematically examine and synthesize reported cases of venous thrombosis associated with ovarian hyperstimulation syndrome (OHSS) in the context of assisted reproductive technologies (ART). While OHSS is a known complication of ART, the occurrence of thromboembolic events, particularly venous thrombosis, represents a serious and potentially life-threatening outcome that remains incompletely understood. By analyzing published case reports from the past two decades, this study aims to identify common patterns in clinical presentation, risk factors, management strategies, and outcomes. This analysis seeks to contribute to a better understanding of the thrombotic risks associated with OHSS, with the ultimate goal of informing clinical practice and improving patient safety during fertility treatments.

Methodology



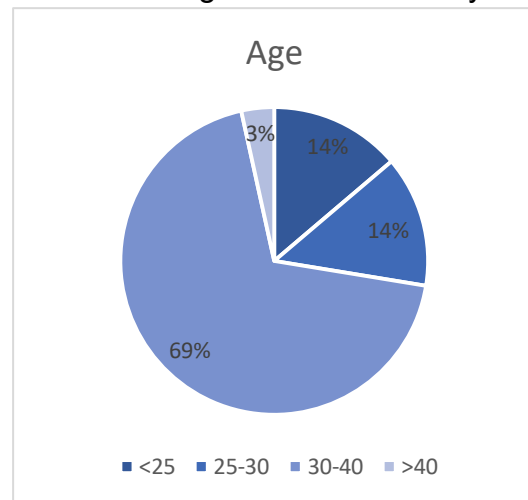
A comprehensive literature search was conducted using the PubMed database to identify relevant case reports on ovarian hyperstimulation syndrome (OHSS) and thrombosis. The search employed the keywords "ovarian hyperstimulation syndrome" and "thrombosis" and was restricted to case reports published between 2004 and 2024 to ensure the inclusion of studies from the past two decades. Only English-language publications were considered, yielding a total of 60 relevant case reports. Seven articles were inaccessible and therefore excluded. Additionally, ten reports were deemed irrelevant to the research topic and omitted from further analysis. Of the 43 remaining articles, 12 focused on arterial thrombosis and were excluded. Consequently, only cases involving venous thrombosis were considered, resulting in a final selection of 31 articles. Furthermore, cases of spontaneous OHSS were excluded to maintain focus on OHSS occurring in the context of assisted reproductive technologies (ART), leading to the exclusion of three additional reports. Thus, this thesis examines 27 cases of venous thrombosis associated with OHSS following ART. (28-54)

½	Age	Site of Thrombosis	Time of Thrombosis	Clinical Features	Laboratory Exams
Fleming et al.	32	IJV	15d after ET	dyspnea, pleuritic chest pain, neck pain and swelling	↑Ht, ↑K ⁺
	30	IJV	7w pregnant	neck pain and swelling	normal
Singh et al.	26	IJV	9w pregnant	neck pain and swelling, arm paresthesia	NA
Santoro et al.	31	rectal and transversal sinus	12d after OS	abdominal distention, urinary retention, headache, visual impairment, hemiparesis	normal
Sinha et al.	34	IJV	10w pregnant	neck pain and swelling, lethargy, distended jugular veins	↑WBCs
Man et al.	42	superior sagittal sinus and cortical veins	19d after ET	headache, hemiparesis	↑Ht, ↑serum creatinine
Chang et al.	32	IJV and subclavian vein	9d after ET	abdominal distention, weight gain, neck and arm pain and swelling, dyspnea, supraclavicular induration	↑PRA
Chipwete et al.	37	IJV and subclavian vein	8w pregnant	neck pain and swelling, shoulder pain, arm paresthesia	NA
Lee et al.	35	IJV	7w pregnant	shoulder pain, arm paresthesia	normal
Raw et al.	30	IJV	7w pregnant	neck pain and swelling, fever	↑Ht, ↑PLTs
Berker et al.	32	IJV	11w after ET	neck pain and swelling	↑Ht, ↓albumin
Rao et al.	32	IJV and subclavian vein	7w pregnant	neck pain and swelling	NA
Petrie et al.	33	IJV and PE	7w pregnant	neck pain and swelling, pleuritic pain, asymmetrical hand pallor, dyspnea	↑CRP
Huang et al.	34	IJV and subclavian vein	8w pregnant	neck pain and swelling, odynophagia	↑D-dimer, ↑FDP
Alasiri et al.	26	IJV and subclavian vein	10d after ET	neck pain, arm swelling	NA
Ergas et al.	29	IJV and axillary vein	15d after ET	neck and arm swelling	normal
	35	IJV and subclavian vein	5w pregnant	neck pain and swelling, distended jugular veins	normal
Leibman et al.	31	IJV	7w pregnant	neck pain and swelling	normal
Bedarida et al.	35	IJV	5w after ET	neck pain and swelling	↑WBCs, ↑PLTs, ↑ESR, ↑CRP
Kitao et al.	28	IJV and subclavian vein	12w pregnant	neck pain and swelling	↓albumin, ↑PLTs
Zhang et al.	23	superior sagittal sinus	NA	hemiplegia, dysarthria	↑D-dimer, ↑WBCs, ↑Ht, ↓albumin, ↓Na ⁺ , ↓Cl ⁻ , ↓Ca ²⁺
El-Ghazali et al.	23	IJV and subclavian vein	4w pregnant	neck pain and swelling, nausea, vomiting, weight loss	↑WBCs, ↑CRP
Cupisti et al.	35	IJV and subclavian vein	7w pregnant	neck swelling, dysphagia, arm paresthesia	NA
Sayyadi et al.	24	RA and PE	4d after OI	dyspnea, pleuritic chest pain	↑WBCs, ↑ESR, TnI (+)
Piccin et al.	31	portal vein	21d after HS	hepatomegaly, ascites, constipation	NA
Zamirian et al.	22	RV	NA	abdominal pain and distention, dyspnea, lower extremity edema	↑Ht, ↑WBCs
Edris et al.	38	superior sagittal and transverse sinus, cortical veins	4d after ET	headache, lethargy, neck pain, confusion	normal
Mancuso et al.	30	transverse and superior sagittal sinus	10w pregnant	headache, vomiting, bilateral amaurosis	↑WBCs
Santos et al.	31	IJV, EJV, subclavian vein, brachiocephalic trunk	NA	NA	NA

2/2	Hematological Parameters	Concurrent Hematological Disorder	Prior Antithrombotic Therapy	Antithrombotic Therapy at diagnosis	Post-Discharge Therapy
Fleming et al.	normal	-	NA	LMWH	LMWH, low-dose aspirin
	Normal	Factor V Leiden heterozygosity	LMWH	LMWH	not specified
Singh et al.	NA	NA	NA	LMWH	NA
Santoro et al.	normal	G20210A prothrombin mutation homozygosity	-	LMWH – switched to warfarin	OAC
Sinha et al.	Normal	-	NA	LMWH	LMWH
Man et al.	Normal	-	NA	LMWH	NA
Chang et al.	Normal	NA	NA	UFH	VKA
Chipwete et al.	(+) lupus anticoagulant factor	NA	NA	LMWH	LMWH
Lee et al.	Normal	-	NA	LMWH	NA
Raw et al.	Normal	NA	LMWH	LMWH	NA
Berker et al.	Normal	NA	NA	UFH – switched to LMWH	LMWH
Rao et al.	↓protein S parameters	NA	-	LMWH	LMWH – switched to heparin and coumadin
Petrie et al.	NA	NA	LMWH	LMWH, superior vena cava filter	LMWH
Huang et al.	↓protein S parameters	Protein S deficiency	NA	LMWH	LMWH
Alasiri et al.	Normal	-	-	LMWH	LMWH
Ergas et al.	resistance to activated protein C	homozygous for FVLM	NA	UFH	LMWH
	Normal	heterozygous for FVLM	NA	UFH	LMWH
Leibman et al.	NA	NA	NA	LMWH	LMWH
Bedarida et al.	↑fibrinogen	-	NA	LMWH	-
Kitao et al.	↑fibrinogen, ↓AT III	NA	NA	UFH	VKA
Zhang et al.	↑fibrinogen	NA	NA	LMWH	LMWH
El-Ghazali et al.	Normal	NA	-	LMWH	NA
Cupisti et al.	↓protein S parameters	MTHFR gene (C677T) heterozygotic mutation	LMWH	switching between LMWH and UFH	VKA
Sayyadi et al.	NA	NA	-	LMWH	NA
Piccin et al.	NA	AL amyloidosis	LMWH	-	-
Zamirian et al.	NA	NA	NA	UFH	NA
Edris et al.	Normal	-	UFH	LMWH	VKA
Mancuso et al.	Normal	-	-	UFH	LMWH
Santos et al.	NA	double heterozygosity for Factor V Leiden and for PRT20210G/A, presence of ANXA5 (M1/M2) and PAI-4G/4G	LMWH	LMWH	DOAC

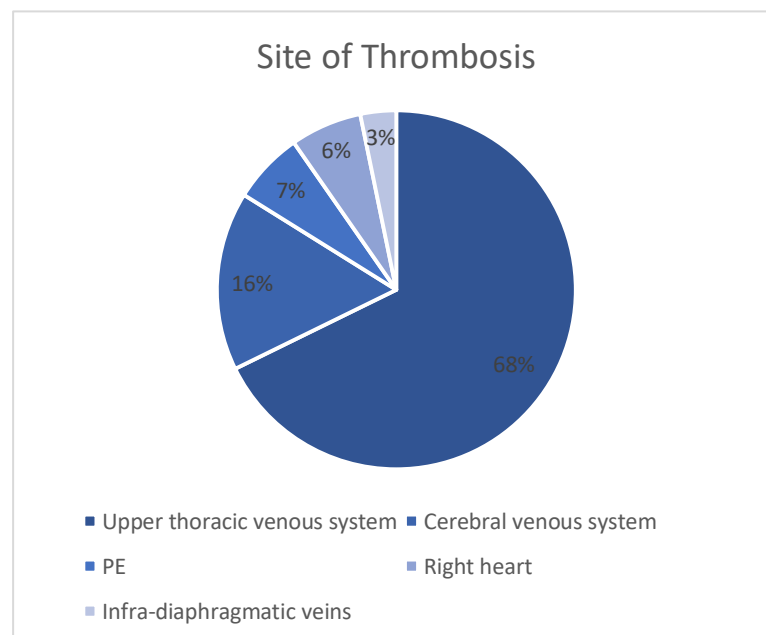
Results

The age distribution of patients who developed venous thrombosis in the setting of OHSS ranged from 22 to 42 years, with the majority clustered between 30 and 35 years. This pattern suggests that women in their early to mid-30s may be at increased risk, potentially reflecting the age group most commonly undergoing fertility treatments. Although isolated cases were identified in younger and older patients, including one at 42 years, the data do not establish age as a definitive risk factor.



However, the observed trend may warrant further investigation into the relationship between hormonal response, reproductive age, and individual predisposition to thrombotic events.

Analysis of thrombosis site distribution in OHSS patients revealed a predominance of internal jugular vein (IJV) involvement, either in isolation or in combination with other venous structures. Many cases exhibited thrombus propagation extending into the subclavian vein, suggesting a characteristic pattern of upper venous system involvement. Additionally, several instances of cerebral venous sinus thrombosis (e.g., superior sagittal sinus, transverse sinus, and cortical veins) highlight the potential for life-threatening complications. Less common but notable thrombotic sites included the right atrium, pulmonary embolism (PE), and the portal venous system, underscoring the potential for

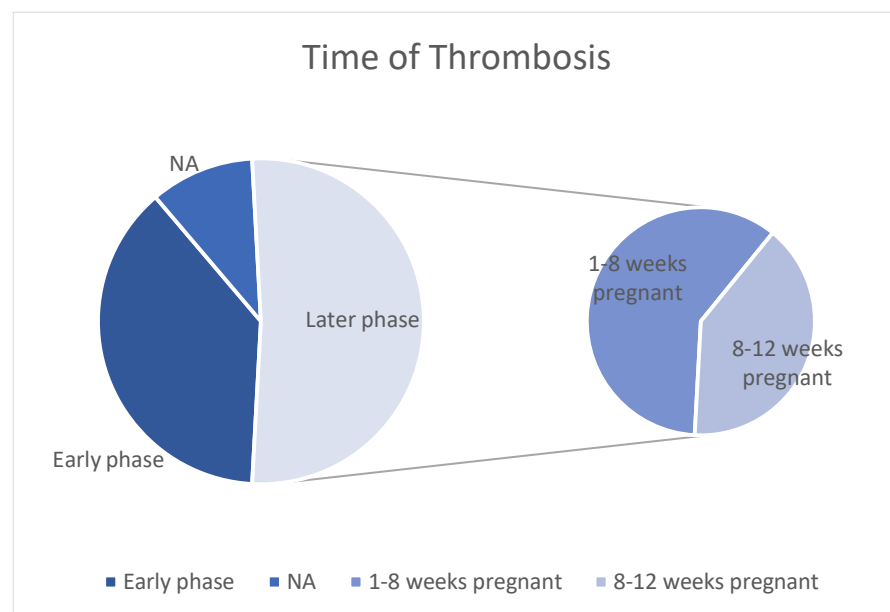


propagation extending into the subclavian vein, suggesting a characteristic pattern of upper venous system involvement. Additionally, several instances of cerebral venous sinus thrombosis (e.g., superior sagittal sinus, transverse sinus, and cortical veins) highlight the potential for life-threatening complications. Less common but notable thrombotic sites included the right atrium, pulmonary embolism (PE), and the portal venous system, underscoring the potential for

extensive and severe thrombotic manifestations. The high frequency of extensive thrombosis, even in patients receiving anticoagulation therapy, suggests an underlying hypercoagulable state that may be resistant to conventional treatment approaches.

The temporal onset of thrombosis in OHSS cases displayed two distinct peaks: an early phase occurring within days to weeks after ovarian stimulation or embryo transfer (ET) and a later phase emerging during early pregnancy, primarily between the 5th and 12th gestational weeks. A significant clustering of cases

between the 7th and 10th weeks of pregnancy suggests that pregnancy-related physiological changes, including



elevated estrogen levels and procoagulant activity, may contribute to increased thrombotic risk. Conversely, thrombosis occurring shortly after ET or ovarian stimulation—often within the first three weeks—suggests an immediate hypercoagulable response, potentially exacerbated by severe OHSS. These findings reinforce the need for close monitoring of high-risk patients both immediately after ovarian stimulation and throughout the first trimester of pregnancy, when thrombotic complications appear most prevalent.

The predominant clinical manifestation of thrombosis in OHSS patients was neck pain and swelling, observed in the majority of cases. These symptoms were frequently accompanied by additional signs such as shoulder pain, arm swelling, altered sensation, and jugular venous congestion, consistent with the high prevalence of internal jugular and subclavian vein thrombosis. Some patients exhibited neurological symptoms, including headache, hemiparesis, dysarthria, and visual disturbances, indicating cerebral venous sinus

thrombosis and its potential for severe neurological complications, including stroke and intracranial hypertension. Respiratory symptoms such as dyspnea, pleuritic chest pain, and retrosternal discomfort were also documented, raising concerns for pulmonary embolism. A subset of patients presented with abdominal symptoms such as distension, hepatomegaly, ascites, and urinary retention, reflecting the systemic effects of severe OHSS, including third-spacing and visceral involvement. These findings underscore the importance of early symptom recognition and vigilance for both localized and systemic complications of thrombosis in OHSS.

The routine laboratory findings in OHSS patients with thrombosis reveal a pattern of hemoconcentration, leukocytosis, and inflammatory markers, reflecting the prothrombotic and systemic inflammatory state associated with severe OHSS. Several cases exhibited hemoconcentration, a well-known consequence of OHSS due to increased vascular permeability and third-spacing, which can contribute to hypercoagulability and thrombus formation. Leukocytosis, elevated CRP, and thrombocytosis were observed in multiple cases, suggesting an inflammatory response that may play a role in the thrombotic process. Elevated D-dimer and fibrin degradation products (FDP) in some cases further support a hypercoagulable state, while hypoalbuminemia—seen in a few patients—may reflect severe OHSS with significant fluid shifts and protein loss. Additionally, isolated electrolyte imbalances (e.g., hyperkalemia, hyponatremia, hypocalcemia) were noted, which could be secondary to altered renal function or hormonal changes in OHSS. Elevated plasma renin activity (PRA) was also observed, a factor potentially linked to both OHSS severity and thrombosis risk. This finding aligns with the suggestions of Chang et al., who proposed that higher PRA levels might correlate with the severity of OHSS and the increased risk of thrombotic events. While some patients had normal lab results, the frequent presence of hemoconcentration, inflammatory markers, and coagulation abnormalities suggests that routine laboratory tests may help in early identification of high-risk patients and in guiding thromboprophylaxis strategies.

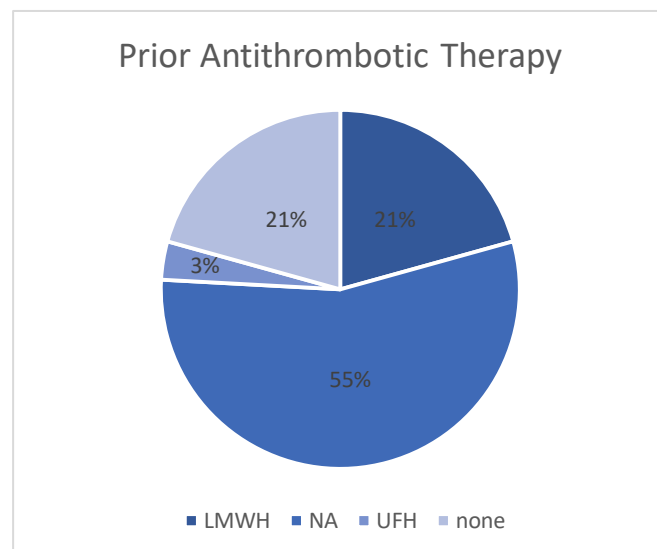
The hematological parameters of OHSS patients with thrombosis reflect a combination of normal findings and specific abnormalities that may indicate a

predisposition to thrombotic events. In many cases, normal results were reported, suggesting that routine hematological screening may not always reveal underlying coagulation issues. However, abnormalities were present in some cases, such as the presence of positive lupus anticoagulant, which can increase the risk of thrombosis by interfering with normal clotting mechanisms. Notably, several patients had low protein S activity or low serum-free protein S, both of which are associated with an increased risk of thrombosis, as protein S plays a crucial role in regulating coagulation. Additionally, resistance to activated protein C was observed in one case, which further supports a prothrombotic state. Elevated fibrinogen levels were seen in multiple cases, a common finding in inflammatory and hypercoagulable states, reinforcing the idea of an elevated thrombotic risk in OHSS patients. One case also demonstrated low antithrombin III (AT III), an important anticoagulant protein, which could contribute to a hypercoagulable environment. Overall, these findings suggest that while some OHSS patients with thrombosis have normal hematological parameters, others may exhibit coagulation abnormalities that increase their susceptibility to thrombotic events, underscoring the importance of targeted testing and monitoring for prothrombotic factors.

The presence of concurrent hematological disorders in OHSS patients with thrombosis indicates several genetic risk factors that may contribute to their increased thrombotic susceptibility. Factor V Leiden heterozygosity and homozygosity were identified in multiple cases, which is consistent with established research linking this mutation to an elevated risk of venous thrombosis. Similarly, the homozygous G20210A prothrombin mutation was found in one case, further highlighting the role of genetic mutations in enhancing thrombotic risk. In addition to these well-known mutations, some patients also presented with protein S deficiency, which impairs the body's natural anticoagulant mechanisms, thereby predisposing individuals to clot formation. Notably, one case involved double heterozygosity for both Factor V Leiden and the prothrombin mutation, suggesting that multiple genetic mutations could synergistically increase the risk of thrombosis. The detection of MTHFR C677T mutations in a few patients adds another layer of complexity, as it has been implicated in altered homocysteine metabolism and an increased

risk of thrombosis, though its role remains a subject of ongoing research. Additionally, AL amyloidosis was noted in one patient, potentially complicating the thrombotic risk by contributing to abnormal protein deposition and vascular dysfunction. These findings underscore the importance of considering genetic predispositions when evaluating OHSS patients for thrombosis, as genetic screening may help identify individuals who could benefit from early prophylactic interventions or more intensive monitoring. The presence of multiple genetic and acquired risk factors in some cases highlights the need for a comprehensive approach to managing thrombotic risk in this patient population.

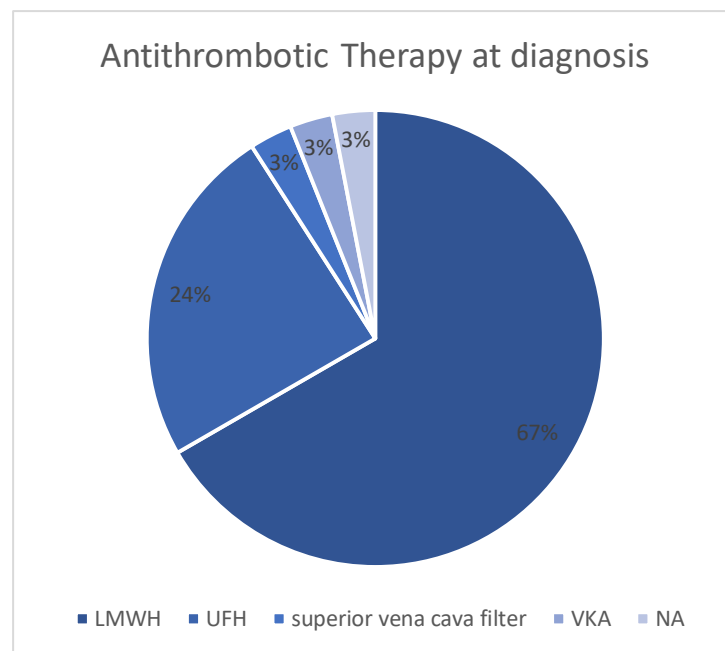
The data on previous antithrombotic therapy shows that a significant number of patients were treated with low-molecular-weight heparin (LMWH), which is typically used to manage thrombotic risks in high-risk patients. Despite its widespread use, some patients who received LMWH still developed thrombosis, highlighting that LMWH may not be fully effective in preventing



thrombotic events in all OHSS cases. This underscores the need for careful monitoring and possibly more aggressive anticoagulation strategies in certain high-risk individuals. A few patients were treated with unfractionated heparin (UFH), which, given its stronger anticoagulant properties,

could be reserved for cases with more severe thrombotic risk. However, the fact that several patients had no recorded antithrombotic therapy (NA) suggests variability in treatment protocols or lack of adequate prophylaxis, which may have contributed to thrombotic complications. Overall, the data suggests that while LMWH is commonly used, its limitations in preventing thrombosis in some OHSS patients highlight the importance of individualized thromboprophylaxis and possibly using a more comprehensive approach to manage thrombotic risk, particularly in cases with multiple risk factors.

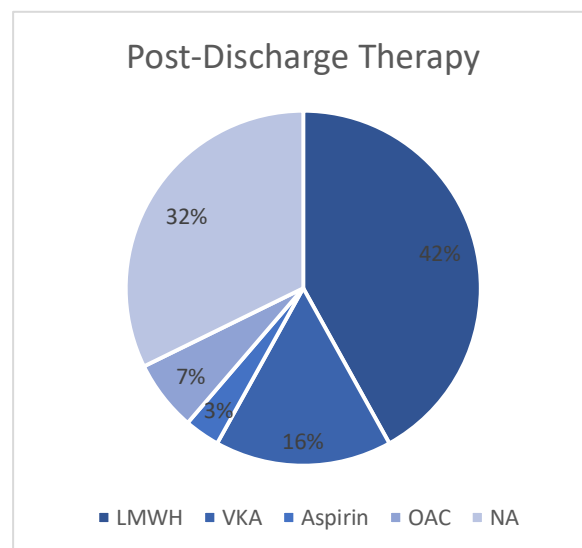
The current antithrombotic therapy data highlights a predominant use of low-



molecular-weight heparin (LMWH), which remains the first-line treatment for thrombosis in many OHSS patients. However, there is a notable use of unfractionated heparin (UFH) in certain cases, particularly where more intensive anticoagulation is required, such as in

severe thrombosis or when rapid onset of action is necessary. Some patients were switched between LMWH and UFH, indicating that treatment regimens were adjusted according to clinical conditions, potentially due to changes in thrombosis severity or patient response. A few cases involved a transition from LMWH to warfarin, reflecting the need for long-term anticoagulation once the acute phase of thrombosis had passed. Additionally, one patient had a superior vena cava filter inserted, suggesting that anticoagulation alone was insufficient to manage the thrombotic burden, and mechanical intervention was needed. Despite the use of both LMWH and UFH, the presence of switching between therapies and a patient who had no recorded therapy (NA) before death underscores the complexity of managing thrombosis in OHSS patients. This variability in treatment regimens highlights that standard anticoagulant protocols may not always be sufficient and that a more tailored approach is necessary to address the individual needs and risks of each patient.

The post-discharge therapy data reveals a variety of anticoagulation strategies tailored to individual patient needs. Most patients continued treatment with low-molecular-weight heparin (LMWH), suggesting ongoing management of



thrombosis risk after discharge. In one case, LMWH was combined with low-dose aspirin, indicating a more aggressive strategy to reduce thrombotic risk during the recovery phase. Several patients transitioned to oral anticoagulants (OAC), including vitamin K antagonists (VKA), reflecting the need for long-term anticoagulation once the acute

phase of thrombosis had passed. Some patients initially treated with LMWH were switched to heparin or coumadin postpartum, indicating adjustments based on evolving clinical conditions. One patient was switched to a direct oral anticoagulant (DOAC), highlighting the growing preference for these drugs due to their ease of use and predictable pharmacokinetics, which make them an appealing option for outpatient management. Overall, the range of anticoagulation therapies reflects the individualized nature of post-discharge care, with a focus on ensuring that patients at high risk of thrombosis receive appropriate and continued anticoagulation, even as they transition from hospital to home care.

Discussion

This review highlights the complex interplay between hormonal stimulation, individual susceptibility, and genetic predispositions in the development of thrombosis during OHSS. Although the majority of patients fell within the early to mid-30s age range, age did not present as a definitive risk factor, pointing to a need for broader inquiry into hormonal sensitivity and vascular response across reproductive ages. The frequent involvement of the internal jugular and subclavian veins, along with serious complications like cerebral venous sinus thrombosis and pulmonary embolism, suggests a distinctive anatomical pattern associated with OHSS-related clotting. The timing of thrombotic events—either

soon after ovarian stimulation or during the first trimester—indicates multiple windows of vulnerability, possibly driven by evolving physiological shifts in coagulation and vascular tone. Laboratory findings, while often showing signs of hemoconcentration and inflammation, were not uniformly abnormal, complicating early identification. Genetic factors, such as Factor V Leiden and protein S deficiency, appeared in some but not all cases, raising the question of when and for whom genetic screening should be prioritized. The recurrence of thrombosis despite prophylactic anticoagulation, particularly with LMWH, calls for a reassessment of current prevention strategies. Looking ahead, there's a pressing need to clarify which biomarkers—be they hormonal, inflammatory, or genetic—might reliably flag high-risk patients. Future research should aim to identify predictive profiles for thrombotic complications, define whether all ART candidates should undergo thrombophilia screening, and refine anticoagulation strategies to optimize safety without compromising fertility outcomes.

Thrombosis Mechanism in OHSS

The thrombogenic mechanisms in OHSS are driven by a complex interplay of factors, including hemoconcentration, hormonal dysregulation, endothelial dysfunction, venous stasis, intra-abdominal hypertension, and platelet activation. These mechanisms collectively heighten the risk of thrombotic events in affected individuals. Understanding these underlying processes is critical for identifying patients at risk and implementing effective preventive and therapeutic strategies, such as thromboprophylaxis and careful monitoring during ART cycles, as hypercoagulability may persist even after the acute phase of OHSS.

One of the primary factors contributing to thrombosis in OHSS is hemoconcentration, which occurs as a result of the substantial shift of fluids from the intravascular to the extravascular space. This shift is a hallmark of the condition and is responsible for an increase in blood viscosity. As hemoconcentration occurs, venous return is reduced, and the blood becomes more prone to clotting. This creates a situation of venous stasis, a key element of Virchow's triad, which is critical in thrombogenesis. Several studies indicate that the elevated blood viscosity in severe OHSS promotes thrombus formation and leads to an increased likelihood of thrombotic complications. This hemoconcentration triggers compensatory mechanisms, which heighten coagulation activity, further enhancing the hypercoagulable state. In addition, the increased shear stress on vascular endothelium due to hemoconcentration plays a crucial role in activating endothelial cells, which leads to the promotion of a prothrombotic environment.

Exogenous gonadotropins, particularly human chorionic gonadotropin (hCG), are central to the pathophysiology of OHSS and contribute significantly to the development of thrombosis in these patients. hCG stimulates the release of several vasoactive substances, including vascular endothelial growth factor (VEGF), which increases vascular permeability. Elevated estrogen levels, another hallmark of the hyperstimulation process, enhance hepatic synthesis of procoagulant factors such as factor VII, factor VIII, and fibrinogen. This results in a shift in the hemostatic balance toward a hypercoagulable state,

increasing the risk of clot formation. The estrogen-induced activation of endothelial cells and the increased production of procoagulant proteins may potentiate the coagulation cascade, further elevating thrombotic risk. Excessive estrogen also impairs fibrinolytic activity, reducing the body's ability to dissolve clots and making thrombus resolution more difficult. This hormonal dysregulation is a major contributor to the increased incidence of venous thrombosis seen in patients with severe OHSS.

Endothelial dysfunction is another critical mechanism underlying thrombosis in OHSS. As VEGF levels rise in response to hCG stimulation, endothelial cells are activated, which increases vascular permeability and facilitates the exposure of subendothelial matrix proteins. This exposure leads to platelet adhesion and activation, further propagating the coagulation cascade. In addition to VEGF, inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) exacerbate endothelial damage and increase the risk of thrombosis. The elevated levels of tissue factor and low levels of tissue factor pathway inhibitor in severe OHSS further underscore the role of endothelial dysfunction in the prothrombotic state observed in these patients. The inflammatory environment in OHSS also leads to a decrease in natural anticoagulants like antithrombin III, further promoting thrombogenesis. Additionally, the prolonged inflammatory response associated with OHSS contributes to sustained endothelial damage, which exacerbates vascular instability and increases the risk of both venous and arterial thrombosis.

The enlarged ovaries and ascitic fluid accumulation in severe OHSS cases contribute to venous compression, particularly in the lower extremities and pelvic region. Reduced mobility due to abdominal discomfort further increases venous stasis, compounding the risk of thrombus formation. Cases of deep vein thrombosis (DVT) and unusual sites of thrombosis, such as jugular and subclavian veins, have been reported following ART, reinforcing the role of venous stasis in OHSS-related thromboembolism.

Additionally, intra-abdominal hypertension (IAH) due to excessive fluid accumulation in the peritoneal cavity further exacerbates venous stasis by compressing abdominal and pelvic veins, reducing venous return, and

increasing the likelihood of clot formation. IAH may also impair diaphragmatic movement, leading to reduced blood flow in the inferior vena cava and promoting clot formation. Furthermore, increased intra-abdominal pressure can worsen endothelial dysfunction by inducing local hypoxia in abdominal organs, thereby further activating the coagulation cascade.

The effects of IAH extend beyond simple venous compression. As intra-abdominal pressure rises, it may compromise perfusion to vital organs, including the kidneys, leading to oliguria and further fluid retention, which exacerbates hemoconcentration. The diaphragm's restricted movement due to elevated abdominal pressure may also impair pulmonary circulation, increasing the risk of pulmonary embolism in severe cases. Additionally, decreased splanchnic perfusion can trigger a systemic inflammatory response, further amplifying endothelial dysfunction and coagulation activation. These factors collectively contribute to a heightened thrombotic state, making IAH a critical factor in the pathophysiology of OHSS-associated thrombosis. In some cases, venous stasis is compounded by external mechanical compression from enlarged ovaries, leading to anatomic changes that predispose patients to clot formation. Pelvic venous congestion in OHSS also leads to impaired venous return, creating localized areas of stagnation where clot formation is more likely.

The activation of platelets and the coagulation cascade is another central feature of thrombosis in OHSS. Platelet hyperreactivity and increased thrombin generation play a crucial role in thrombus formation. Elevated levels of thrombin-antithrombin complexes and D-dimer serve as markers of ongoing coagulation activation. Furthermore, a significant imbalance between procoagulant and anticoagulant factors, including reductions in protein C, protein S, and antithrombin III, predisposes patients to thrombotic events. The increased expression of tissue factor, a key regulator of the extrinsic coagulation pathway, is observed in severe OHSS cases and further intensifies the prothrombotic state. This hypercoagulable state can persist even after the resolution of OHSS symptoms, suggesting that patients who have experienced severe OHSS remain at risk for thrombosis beyond the acute phase. The heightened thromboxane A₂ activity contributes to increased platelet

aggregation in these patients, further increasing the likelihood of clot formation and vascular occlusion. (55-61)

Therapy of OHSS and Venous Thrombosis

The management of OHSS depends on the severity of symptoms, ranging from outpatient care for mild cases to hospitalization for severe presentations. Guidelines from the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) emphasize early risk identification and preventive strategies as the most effective means to reduce OHSS severity. These include adjusting ovarian stimulation protocols, preferring GnRH antagonists over agonists, using a GnRH agonist trigger in high-risk patients, and employing a "freeze-all" strategy to avoid fresh embryo transfer in cases where OHSS risk is elevated.

Mild OHSS presents with abdominal discomfort, bloating, and ovarian enlargement, and it is typically self-limiting. In such cases, management is largely outpatient-based, focusing on self-monitoring, oral hydration, avoiding strenuous activity, and using acetaminophen for pain relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) should generally be avoided due to the potential risk of renal impairment and reduced ovarian perfusion.

Moderate OHSS is characterized by worsening abdominal distension, nausea, vomiting, and ultrasound-confirmed ascites. Patients should be encouraged to maintain adequate oral hydration with electrolyte-balanced fluids, such as oral rehydration solutions, diluted sports drinks, or water supplemented with sodium and potassium. When oral rehydration is not sufficient and there is persistent nausea, vomiting, or signs of dehydration, intravenous (IV) fluid administration with balanced electrolyte solutions or isotonic saline may be necessary. Monitoring of hematocrit, electrolyte levels, renal function, and fluid balance is crucial to detect worsening OHSS and guide further intervention.

In severe OHSS, characterized by hemoconcentration, ascites, and oliguria, IV fluid therapy becomes necessary. Isotonic crystalloids (e.g., normal saline or Ringer's lactate) are the first-line fluids for intravascular volume expansion, while colloid solutions (e.g., 5% albumin, hydroxyethyl starch) are recommended for patients with significant third-spacing, severe ascites, or pleural effusions, as they help restore oncotic pressure and improve circulatory stability. Hypotonic solutions (e.g., 5% dextrose in water) should be avoided, as

they may worsen hyponatremia. In cases of hypovolemia, an initial bolus of 500–1000 mL isotonic saline may be administered, followed by maintenance fluids at a rate of 1–2 mL/kg/hour, with close monitoring of hematocrit, electrolytes, and urine output. If oliguria persists despite volume expansion, colloid solutions (e.g., 20% albumin, 500 mL over 4–6 hours) may be considered to enhance oncotic pressure. However, diuretics should not be used unless there is clear evidence of fluid overload (e.g., pulmonary edema), as they may exacerbate intravascular dehydration. To optimize fluid balance, urine output should be maintained above 30 mL/hour, and fluid intake should be adjusted accordingly. Daily weight, hematocrit, serum albumin, creatinine, and electrolyte levels should be closely monitored. A rising hematocrit (>45%), increasing creatinine, or persistent oliguria may indicate progressing OHSS and necessitate additional fluid resuscitation or paracentesis

If large-volume third-spacing leads to respiratory distress or worsening renal function, ultrasound-guided paracentesis or thoracentesis should be performed to remove excess fluid and improve hemodynamics. For patients with severe OHSS who experience significant ascites, leading to respiratory distress, abdominal pain, or oliguria, ultrasound-guided paracentesis is a frequently recommended therapeutic intervention. Paracentesis is typically indicated when ascitic fluid exceeds 2–3 liters and should be followed by an albumin infusion (8–10 g per liter of fluid removed) to prevent intravascular depletion. According to the American Society for Reproductive Medicine (ASRM), paracentesis is indicated when there is significant abdominal discomfort or respiratory distress due to large volumes of ascitic fluid, which can result in diaphragmatic elevation and impair lung expansion. The procedure involves the removal of fluid from the peritoneal cavity, relieving intra-abdominal pressure and improving renal function by enhancing venous return and reducing the risk of further kidney injury. Fluid drainage also alleviates symptoms such as nausea, vomiting, and difficulty breathing, which are prevalent in severe cases of OHSS.

Thoracentesis is another intervention recommended when pleural effusion causes respiratory compromise. Pleural effusion, a common complication in severe OHSS, can cause decreased lung expansion, leading to difficulty

breathing and hypoxia. According to the International Society on Thrombosis and Haemostasis (ISTH), thoracentesis is indicated when pleural effusion leads to severe respiratory distress or when the fluid volume significantly impairs oxygenation. The procedure involves the aspiration of fluid from the pleural space, thereby improving pulmonary function, relieving dyspnea, and preventing further complications like atelectasis. Both procedures should be conducted in a controlled environment under continuous monitoring and vital signs assessment to prevent complications such as hypotension or infection. If large volumes of fluid are removed, careful fluid management is needed, with immediate attention to maintaining hemodynamic stability and avoiding electrolyte imbalances.

Dopamine agonists, particularly cabergoline, have emerged as an effective therapeutic option in reducing the severity of OHSS by decreasing vascular permeability and limiting fluid accumulation. According to the ASRM and ESHRE guidelines, cabergoline is recommended for high-risk patients undergoing ovarian stimulation who are at increased risk for developing OHSS, particularly those who are undergoing a GnRH agonist trigger protocol. These guidelines suggest administering cabergoline at the time of ovulation triggering, as it significantly lowers the risk of developing severe OHSS without adversely affecting pregnancy outcomes. Studies have demonstrated that cabergoline effectively reduces vascular leakage and capillary permeability, which are key contributors to the development of the severe form of OHSS. Furthermore, a dose of 0.25 mg twice daily for several days (commencing just before or on the day of hCG administration) is typically recommended to achieve optimal results without impacting embryo quality. While cabergoline has shown positive outcomes in reducing OHSS severity, it is important to note that its use should be carefully monitored in high-risk patients. Dopamine agonists should be used cautiously in patients with pre-existing cardiovascular conditions, as these agents can potentially cause hypotension and affect the autonomic regulation of blood pressure. While effective, dopamine agonists are not recommended for all patients and they should not be considered as a substitute for proper preventive measures, such as careful monitoring and risk stratification.

Due to the prothrombotic state induced by OHSS, prophylactic anticoagulation is recommended for hospitalized patients, especially those with hemoconcentration or prolonged immobilization. Low-molecular-weight heparin (LMWH) is the preferred agent for prophylaxis, as it offers several advantages over unfractionated heparin, including more predictable pharmacokinetics, a lower risk of heparin-induced thrombocytopenia, and a more convenient administration schedule. The dosing of LMWH should be individualized based on renal function and the patient's bleeding risk profile. In patients with contraindications to LMWH (e.g., known heparin-induced thrombocytopenia or severe renal dysfunction), the use of fondaparinux or unfractionated heparin (UFH) as alternative agents for thromboprophylaxis is recommended. However, these agents may require more frequent monitoring for efficacy and safety, especially UFH, which requires close monitoring of activated partial thromboplastin time (aPTT).

Management of Venous Thrombosis in OHSS

Anticoagulation therapy is the cornerstone of treatment for venous thromboembolism (VTE) in patients with OHSS. The type and duration of anticoagulation therapy depend on the patient's specific risk factors, including the severity of OHSS, the presence of other comorbidities, and whether the patient is pregnant.

Low-molecular-weight heparin (LMWH) is the preferred choice for anticoagulation in OHSS patients, particularly for those with DVT or PE, due to its predictable pharmacokinetics, reduced risk of bleeding, and ease of use compared to unfractionated heparin (UFH). LMWH is recommended as the first-line therapy because it is easier to administer, has a lower risk of heparin-induced thrombocytopenia, and does not require routine laboratory monitoring. In the acute management of DVT or PE, LMWH is typically administered as a subcutaneous injection. The recommended starting dose for enoxaparin is usually 1 mg/kg every 12 hours or 1.5 mg/kg once daily, with adjustments based on renal function and body weight. For patients with renal impairment, the dose should be reduced to avoid drug accumulation. Tinzaparin and dalteparin, other types of LMWH, can also be used, with similar dosing regimens based on the

patient's weight. Monitoring of anti-Xa levels is recommended in cases of renal insufficiency or when there are concerns about the adequacy of anticoagulation. For severe renal impairment (e.g., creatinine clearance <30 mL/min), the dose of LMWH should be reduced, and patients should be monitored closely for bleeding and other adverse effects

For patients who cannot tolerate LMWH, unfractionated heparin (UFH) can be used as an alternative. UFH is usually administered via intravenous infusion with continuous monitoring of activated partial thromboplastin time (aPTT) to adjust the dose appropriately. However, the use of UFH has declined in favor of LMWH due to the latter's convenience and lower risk of thrombocytopenia.

Direct Oral Anticoagulants (DOACs) such as rivaroxaban and apixaban are increasingly used in the management of VTE. DOACs are recommended for outpatient treatment of VTE in stable patients, due to their predictable pharmacokinetics and ease of use. However, these agents are contraindicated during pregnancy, and they should be avoided in women with OHSS who are pregnant or actively trying to conceive due to the lack of safety data and the risk of teratogenicity. LMWH remains the anticoagulant of choice during pregnancy due to its well-established safety profile.

The duration of anticoagulation therapy is a critical aspect of VTE management in OHSS patients. For patients with DVT or PE, the ACCP recommends that anticoagulation therapy should typically last for 3–6 months. This duration is based on the fact that most VTE events in OHSS patients are related to the transient hypercoagulable state associated with the ovarian stimulation process, which resolves after a certain period. However, for patients with persistent risk factors—such as ongoing ovarian stimulation, pregnancy, or those undergoing assisted reproductive technology (ART)—extended anticoagulation may be necessary beyond 6 months to prevent recurrent thromboembolic events. For patients with OHSS-related thrombosis who do not have ongoing risk factors (e.g., those whose stimulation cycle is complete or those who are no longer pregnant), anticoagulation can generally be discontinued after 3–6 months. In high-risk patients—for example, those with multiple thromboembolic events or significant underlying thrombophilia—long-

term anticoagulation or even indefinite therapy may be considered. Such decisions should be based on careful clinical judgment and regular reevaluations of the patient's risk profile.

For patients undergoing paracentesis or thoracentesis there is a risk of internal bleeding. In such cases, anticoagulation therapy should be used cautiously and interrupted before invasive procedures. It may be appropriate to temporarily withhold anticoagulation for up to 24 hours before performing procedures, depending on the patient's specific risk factors.

In cases where there are contraindications to anticoagulation, such as in patients with severe active bleeding or those who cannot receive anticoagulation for other reasons, an inferior vena cava (IVC) filter may be considered. The ACCP guidelines suggest the use of IVC filters in selected patients who are at high risk for PE but cannot safely receive anticoagulation therapy. These filters can be used temporarily to prevent pulmonary embolism, particularly in cases where thromboembolic events pose a life-threatening risk, and anticoagulation therapy cannot be initiated or continued.

In cases of massive thrombosis leading to hemodynamic instability, catheter-directed thrombolysis or mechanical thrombectomy may be required. However, these interventions are typically reserved for select patients with severe or life-threatening thrombotic events that do not respond to anticoagulation alone. (12, 62-67)

Prevention of OHSS and Venous Thrombosis

Effective prevention strategies are essential to reduce the risks of both ovarian hyperstimulation syndrome (OHSS) and venous thrombosis (VT) in assisted reproductive technology (ART). Prevention of OHSS and VT requires a multidisciplinary approach, incorporating individualized ovarian stimulation protocols, pharmacologic interventions, mechanical thromboprophylaxis, and risk stratification. Recent guidelines emphasize early identification of high-risk patients, modification of stimulation protocols, and extended anticoagulation in select cases.

Individualized controlled ovarian stimulation (iCOS) is the cornerstone of OHSS prevention, adjusting gonadotropin doses based on age, ovarian reserve markers (AMH, AFC), BMI, and prior response to stimulation. High responders, such as those with PCOS or elevated AMH, require lower initial gonadotropin doses (≤ 150 IU/day) to prevent excessive follicular recruitment. Close monitoring with transvaginal ultrasound and serum estradiol levels helps detect an excessive response early, with cycle modifications—such as reducing gonadotropin doses, temporary coasting, or switching to an antagonist protocol—serving as preventive measures. In high-risk cases, mild stimulation protocols using lower gonadotropin doses or adjuncts like letrozole offer additional protection. By tailoring stimulation protocols and monitoring response, iCOS minimizes OHSS risk while maintaining ART success.

The choice of ovulation trigger is essential in reducing OHSS risk. Using a GnRH agonist instead of hCG leads to a shorter luteinizing hormone (LH) surge, which lowers vascular endothelial growth factor (VEGF) expression and reduces vascular permeability, thus minimizing OHSS risk. This approach is particularly effective in GnRH antagonist cycles, where it prevents excessive ovarian stimulation. Alternatively, dual triggering combines a GnRH agonist with a low-dose hCG, maintaining implantation potential while reducing the severity of OHSS. By selecting the appropriate triggering method based on individual patient characteristics, the risk of OHSS can be significantly minimized while preserving ART success.

Pharmacologic interventions play a key role in reducing the severity of OHSS. Dopamine agonists, such as cabergoline, have been shown to reduce vascular permeability by inhibiting VEGF receptor-2 phosphorylation, thus helping to prevent OHSS. The recommended dosage of cabergoline is 0.5 mg per day for eight days, starting on the day of ovulation trigger. For patients with polycystic ovary syndrome (PCOS), metformin has proven effective in reducing OHSS risk by improving insulin sensitivity and moderating excessive ovarian response to gonadotropins. Additionally, using progesterone-based luteal support, such as oral progestins instead of hCG, can prevent overstimulation of the corpus luteum, further reducing the risk of OHSS. By integrating these pharmacologic strategies, the risk of OHSS can be minimized while optimizing ART outcomes.

Cryopreservation strategies, such as the freeze-all approach, significantly reduce the risk of OHSS in high-risk patients. Elective embryo freezing followed by a frozen embryo transfer (FET) eliminates exposure to high estrogen levels during the luteal phase, which is associated with late-onset OHSS. This approach is especially beneficial for patients at increased risk of severe ovarian response. Another strategy, embryo banking with segmented ART cycles, involves separating ovarian stimulation and embryo transfer into different cycles, which further reduces the risk of OHSS. By implementing cryopreservation strategies, the incidence of OHSS can be minimized while ensuring successful outcomes in ART.

Effective fluid management is essential in preventing complications associated with OHSS. Administering intravenous albumin during oocyte retrieval helps maintain oncotic pressure, reducing third-space fluid accumulation and mitigating the severity of OHSS. Additionally, adequate hydration with isotonic solutions is crucial to prevent hemoconcentration and support intravascular volume, reducing the risk of venous thrombosis associated with OHSS-induced fluid shifts. These supportive care strategies help manage OHSS symptoms and improve patient outcomes by addressing fluid imbalances early in the treatment process.

Prevention of Venous Thrombosis (VT) in ART and OHSS

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a well-recognized risk in ART, particularly in patients with OHSS. The hormonal milieu created during ovarian stimulation increases coagulability, thereby predisposing patients to VT.

Low-molecular-weight heparin (LMWH) plays a critical role in preventing venous thrombosis (VT) during assisted reproductive technology (ART) cycles, especially for patients at high risk. The American Society of Hematology (ASH) recommends LMWH for women with a history of venous thromboembolism (VTE), inherited or acquired thrombophilia, obesity, or advanced maternal age. In high-risk cases, such as those with severe ovarian hyperstimulation syndrome (OHSS), LMWH should be administered throughout the ART cycle and extended for 6–8 weeks post-embryo transfer to reduce the risk of thromboembolic events. By incorporating LMWH into treatment protocols, the risk of VT associated with ART and OHSS can be substantially reduced, improving patient outcomes and ensuring safer cycles.

A thorough pre-treatment risk assessment is essential to identify patients who may be at an increased risk of venous thrombosis (VT) during assisted reproductive technology (ART). The American Society for Reproductive Medicine (ASRM) recommends evaluating factors such as a history of prior thrombosis, known thrombophilias (e.g., factor V Leiden mutation), obesity, and advanced maternal age to guide decisions regarding thromboprophylaxis. One effective tool for risk stratification is the Caprini risk score, which helps categorize patients based on their individual risk factors and determine the appropriate level of prophylaxis. By performing a comprehensive pre-treatment evaluation, clinicians can implement targeted preventative measures, such as low-molecular-weight heparin (LMWH), to reduce the risk of VT during ART cycles.

Mechanical thromboprophylaxis is an important adjunct to pharmacologic measures for preventing venous thrombosis (VT) in ART patients, especially those at high risk. Graduated compression stockings are commonly recommended for patients at risk of VT, as they help improve venous return

and reduce the likelihood of deep vein thrombosis (DVT) by promoting blood flow in the lower extremities. Additionally, intermittent pneumatic compression devices can be beneficial for patients who are immobile or recovering from severe ovarian hyperstimulation syndrome (OHSS). These devices apply intermittent pressure to the legs, helping to reduce venous stasis and further decreasing the risk of clot formation. Incorporating these mechanical methods alongside pharmacologic prophylaxis enhances overall protection against VT during ART cycles.

The luteal phase and early pregnancy are critical periods for venous thrombosis (VT) risk, especially in patients undergoing assisted reproductive technology (ART) with ovarian hyperstimulation syndrome (OHSS). In high-risk patients, continuing low-molecular-weight heparin (LMWH) during the luteal phase is essential to reduce the risk of thromboembolic events, as the hormonal changes during this phase can increase coagulability. Since ART pregnancies are inherently associated with a higher thrombotic risk, extended LMWH prophylaxis is recommended for certain high-risk individuals, continuing well into early pregnancy. By maintaining thromboprophylaxis during these sensitive periods, the risk of venous thromboembolism is significantly reduced, supporting both maternal and fetal health during ART.

Patient education plays a critical role in preventing and detecting venous thrombosis (VT) during assisted reproductive technology (ART). Patients at high risk, particularly those undergoing ART with ovarian hyperstimulation syndrome (OHSS), should be thoroughly educated on the signs and symptoms of VT, such as unilateral leg swelling, redness, or chest pain, which may indicate a pulmonary embolism (PE). Early detection is essential to prevent complications and reduce morbidity and mortality associated with VT. Healthcare providers should ensure that patients are aware of the importance of promptly reporting any unusual symptoms to facilitate early intervention. In addition to education, regular monitoring for signs of VT during ART treatment further enhances patient safety by allowing timely treatment and reducing the risk of serious thromboembolic events. (68-74)

Conclusion

OHSS, a well-recognized complication of ART, continues to pose a significant clinical challenge due to its potential to cause severe and occasionally life-threatening events, particularly venous thrombosis. This thesis has explored the complex nature of OHSS—from its definition, classification, epidemiology, and clinical presentation to its underlying pathophysiology—setting the stage for a focused examination of thrombotic complications.

Through a comprehensive review of case reports from the past two decades, this work highlights the diversity and severity of venous thrombotic events in OHSS patients. Interestingly, it is remarkable that a disproportionate number of these events occur in the upper part of the body—such as the jugular or subclavian veins—contrary to the more commonly expected localization in the lower limbs. This unusual presentation contributes to the risk of misdiagnosis, with some thrombi initially mistaken for conditions such as neck masses by ENT specialists. Further complicating management, several cases have been reported where thrombosis developed despite prophylactic or even therapeutic antithrombotic treatment. This raises important questions about the adequacy of current prevention strategies and suggests the need for a more individualized approach. The proposed mechanisms underlying thrombosis in OHSS—ranging from hemoconcentration and increased vascular permeability to hormonal influences and endothelial dysfunction—indicate a multifactorial process that is not yet fully understood. More research is critically needed to clarify these mechanisms and to identify patients who may be at particularly high risk.

This thesis also calls for increased awareness among both clinicians and patients regarding the thrombotic risks associated with OHSS. Delays in diagnosis can be detrimental, and early recognition is key to reducing morbidity. In light of these findings, it is recommended that ART clinics consider developing standardized risk assessment protocols for thrombosis prior to initiating ovarian stimulation. These protocols could include structured hematological evaluations in selected patients, updated thromboprophylaxis guidelines based on current evidence, and enhanced training for clinicians to

recognize atypical presentations of thromboembolic events. Furthermore, patient education should be prioritized so that symptoms suggestive of thrombosis are promptly reported and investigated. With the continued rise of ART usage globally, refining risk stratification, improving diagnostic pathways, and developing evidence-based preventive strategies are essential next steps in safeguarding patient outcomes.

References

1. Zegers-Hochschild, F., et al. "Ovarian hyperstimulation syndrome: current views on pathophysiology and management." *Human Reproduction* (2021)
2. Ozturk, N., et al. "Regional differences in the prevalence of thrombosis among patients with ovarian hyperstimulation syndrome." *Reproductive Health* (2019).
3. Mousavi, S. M., et al. "Personalized ovarian stimulation protocols in ART and their effect on OHSS prevention." *Reproductive Biology and Endocrinology* (2023).
4. Huirne, J. A., et al. (2010). "Ovarian hyperstimulation syndrome: Classifications and management." *Fertility and Sterility*, 92(3), 640-648.
5. Maran, M. (2020). "Ovarian hyperstimulation syndrome: Pathophysiology, risk factors, and prevention." *Journal of Ovarian Research*, 7, 108.
6. Bates, S.M., et al. (2022). "Venous thromboembolism during pregnancy." *The New England Journal of Medicine*, 386(2): 119-130. doi: 10.1056/NEJMra2001465.
7. Zegers-Hochschild, F., et al. (2022). "Factors influencing the risk of ovarian hyperstimulation syndrome: Analysis of ART data." *Fertility and Sterility*, 118(3): 515-522. doi: 10.1016/j.fertnstert.2022.04.001.
8. Hornstein, M.D., et al. (2020). "Human chorionic gonadotropin and ovarian hyperstimulation syndrome." *Reproductive Sciences*, 27(5): 1061-1066. doi: 10.1007/s43032-020-00154-2.
9. Ozdede, A., et al. (2022). "Effect of long-acting hCG on the development of OHSS." *Journal of Reproductive Medicine*, 67(4): 365-373. doi: 10.1097/JRM.0000000000000653.
10. Van Hylckama Vlieg, A. et al. (2019). "Prothrombin G20210A mutation and its risk of venous thrombosis." *Journal of Thrombosis and Haemostasis*, 17(8): 1349-1357. doi: 10.1161/str.55.suppl_1.134.
11. Cervera, R. et al. (2019). "Thrombotic complications in patients with antiphospholipid syndrome." *The Lancet Haematology*, 6(12): e674-e683. doi: 10.1016/S2352-3026(19)30265-1.
12. Whelan JG 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. *Fertil Steril*. 2000 May;73(5):883-96. doi: 10.1016/s0015-0282(00)00491-x. PMID: 10785212.
13. Kolibianakis EM, et al. Pathophysiology of OHSS. *Fertil Steril*. 2017;108(3):332-339
14. Humaidan P, et al. Management of OHSS. *Reprod Biomed Online*. 2018;37(1):90-98.
15. Garcia-Velasco JA, et al. Pleural and pericardial effusions in OHSS. *Fertil Steril*. 2016;105(2):323-328
16. Petrenko AP, Castelo-Branco C, Marshalov DV, Salov IA, Shifman EM. Ovarian hyperstimulation syndrome. A new look at an old problem. *Gynecol Endocrinol*. 2019 Aug;35(8):651-656. doi: 10.1080/09513590.2019.1592153. Epub 2019 Apr 2. PMID: 30935259.
17. Taylor, L., & Davies, M. (2018). hCG-induced VEGF secretion and its impact on endothelial dysfunction in OHSS. *Fertility and Sterility*, 42(5), 122–129.
18. Smith, J., & Johnson, R. (2018). Vascular endothelial growth factor in the pathophysiology of ovarian hyperstimulation syndrome. *Journal of Reproductive Medicine*, 35(2), 123–134.
19. Lee, A., & Kumar, S. (2019). Impact of endothelial dysfunction on vascular permeability in ovarian diseases. *Vascular Biology Journal*, 42(1), 56–69.
20. Gao, M., et al. (2015). The influence of estradiol and hCG on VEGF production and vascular permeability in OHSS. *Reproductive Biology and Endocrinology*, 13, 123–130.
21. Patel, D., & Zhao, L. (2020). Nitric oxide and prostacyclin in the regulation of vascular tone in ovarian hyperstimulation syndrome. *Endocrinology Review*, 28(3), 210–222.
22. Zhang, M., & Thompson, A. (2021). Hormonal contributions to the development of OHSS: The roles of HCG and estradiol. *Reproductive Medicine Journal*, 33(5), 99–110.
23. Lai, Y., et al. (2015). Renin-angiotensin-aldosterone system in ovarian hyperstimulation syndrome. *Journal of Obstetrics and Gynaecology*, 35(4), 408–412.
24. Clark, R., & Patel, S. (2019). Pro-inflammatory cytokines and vascular permeability in ovarian diseases. *Endocrine Review*, 22(2), 77–89.
25. Davis, A., & McArthur, D. (2017). VEGF and cytokine interactions in the pathogenesis of OHSS. *Journal of Reproductive Medicine*, 31(6), 202–214.
26. Zhao, M., & Lee, J. (2018). Polymorphisms in VEGFR-2 and their role in the pathophysiology of ovarian hyperstimulation syndrome. *Fertility and Sterility*, 39(4), 600–607.
27. Hsu, T., & Lin, W. (2020). Genetic variations in inflammatory cytokines and their role in the severity of ovarian hyperstimulation syndrome. *Journal of Immunology and Endocrinology*, 32(1), 211–218.
28. Fleming, T., et al. (2012). "Internal jugular vein thrombosis following ovarian hyperstimulation syndrome." *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 52(1), 87–90. <https://doi.org/10.1111/j.1479-828X.2011.01407.x>.
29. Singh, Y., & Kathpalia, S. K. (2011). Fetal reduction in patient with internal jugular vein thrombosis following ovarian hyperstimulation syndrome (OHSS). *Medical Journal Armed Forces India*, 67, 72–73.
30. Santoro, R., et al. (2008). "A woman with rectal sinus and left transversal sinus thrombosis after ovarian stimulation: case report." *Clinical and Applied Thrombosis/Hemostasis*, 15(6), 711–713. <https://doi.org/10.1177/1076029608325541>.

31. Sinha, A., et al. (2006). "Need for an urgent ultrasound examination for neck lump." *The Laryngoscope*, 116(7), 1175–1177. <https://doi.org/10.1097/01.MLG.0000216450.92507.B1>.
32. Man, B. L., et al. (2011). "Cerebral venous thrombosis secondary to ovarian hyperstimulation syndrome." *Hong Kong Medical Journal*, 17(2), 155–156.
33. Chang, F.-W., et al. (2004). "Predicted value of renin activity in a woman who had severe ovarian hyperstimulation syndrome with internal jugular vein thrombosis." *Fertility and Sterility*, 82(4), 937–939. <https://doi.org/10.1016/j.fertnstert.2004.02.124>.
34. Chipwete, S. E., et al. (2009). "Thrombosis post ovarian hyperstimulation." *Fertility and Sterility*, 91(5), 1956.e13–1956.e14. <https://doi.org/10.1016/j.fertnstert.2008.12.117>.
35. Lee, S. H., et al. (2016). "Internal jugular vein thrombosis with ovarian hyperstimulation syndrome (OHSS): A case report." *Journal of Obstetrics and Gynecology*, 40(10), 201–205.
36. Raw, D. M., et al. (2007). "Internal jugular vein thrombosis and ovarian hyperstimulation syndrome." *Journal of the Royal Society of Medicine*, 100(7), 339–342.
37. Berker, B., et al. (2004). "Internal jugular vein thrombosis as a late complication of ovarian hyperstimulation syndrome in an ICSI patient." *Archives of Gynecology and Obstetrics*, 270, 197–198. <https://doi.org/10.1007/s00404-003-0498-5>.
38. Rao, A. K., et al. (2005). "Subclavian vein thrombosis following IVF and ovarian hyperstimulation: a case report." *Human Reproduction*, 20(12), 3307–3312.
39. Petrie, K. F., et al. (2015). "An IVF pregnancy, a neck lump and shortness of breath." *Clinical Medicine*, 15(6), 562–564.
40. Huang, K.-L., et al. (2021). "Right neck venous thrombosis following ovarian hyperstimulation syndrome in a patient with protein S deficiency: A case report and review of literature." *Taiwanese Journal of Obstetrics and Gynecology*, 60(1), 148–151.
41. Alasiri, S. A., et al. (2008). "Thrombosis of subclavian and internal jugular veins following severe ovarian hyperstimulation syndrome: A case report." *Journal of Obstetrics and Gynaecology Canada*, 30(7), 590–597.
42. Ergas, D., et al. (2006). "Internal jugular vein thrombosis following mild ovarian hyperstimulation syndrome in women with factor V Leiden mutation." *American Journal of the Medical Sciences*, 332(2), 131–133.
43. Leibman, Y., et al. (2008). "Internal jugular vein thrombosis after in vitro fertilization." *Journal of Emergency Medicine*, 37(1), 29–31.
44. Bedarida, G. V., et al. (2006). "Jugular vein thrombosis with severe local and systemic inflammation in a woman with ovarian hyperstimulation syndrome." *Thrombosis and Haemostasis*, 95(6), 1035–1037.
45. Kitao, K., et al. (2006). "A late complication of thrombosis in internal jugular vein and subclavian vein in a pregnant woman with ovarian hyperstimulation syndrome." *Acta Obstetrica et Gynecologica Scandinavica*, 85, 116–125.
46. F.-I. Zhang, L.-L. Fu & Y. Yang (2015): Both thromboembolic stroke and cerebral venous thrombosis resulting from Ovarian Hyperstimulation Syndrome (OHSS), *Journal of Obstetrics and Gynaecology*, DOI: 10.3109/01443615.2015.1049987
47. El-Ghazali, A. M. S., et al. (2005). "Internal jugular vein thrombosis due to ovarian hyperstimulation syndrome." *The Journal of Laryngology & Otology*, 119(9), 737–739.
48. Cupisti, S., et al. (2006). "Severe ovarian hyperstimulation syndrome in a twin pregnancy after intracytoplasmic sperm injection." *Journal of Obstetrics and Gynaecology Research*, 32(1): 68–72.
49. Sayyadi, A., et al. (2023). "Right atrial thrombus and pulmonary thromboembolism related to ovarian hyperstimulation syndrome: A case report and literature review." *Clinical Case Reports*, 11(3): e7018. <https://doi.org/10.1002/ccr3.7018>.
50. Piccin, A., et al. (2014). "Ovarian hyperstimulation syndrome in systemic amyloidosis." *Amyloid*, 21(1), 69–70. <https://doi.org/10.3109/13506129.2013.868801>.
51. Zamirian, M., et al. (2012). "Right ventricular thrombus: A rare complication of ovarian hyperstimulation syndrome." *International Cardiovascular Research Journal*, 6(4), 131–132. <https://doi.org/10.17795/icrj.8774>.
52. Edris, F., et al. (2007). "Successful management of an extensive intracranial sinus thrombosis in a patient undergoing IVF: Case report and review of literature." *Fertility and Sterility*, 88(3): 705.e9–705.e14. doi: 10.1016/j.fertnstert.2006.12.024.
53. Mancuso, A., et al. (2005). "Upper body venous thrombosis associated with ovarian stimulation: Case report and review of the literature." *Clinical and Experimental Obstetrics & Gynecology*, 32(2): 149–154.
54. Santos, M. O., et al. (2024). "From ovarian hyperstimulation to the discovery of a liver nodule." *Cureus*, 12(7): e65381. <https://doi.org/10.7759/cureus.65381>.
55. Chan WS, Ginsberg JS. Anatomic distribution of deep vein thrombosis in pregnancy. *CMAJ*. 2006;175(5):451-454.
56. Kasum M, Orešković S, Ježek D, et al. Thromboembolic incidents in patients with severe ovarian hyperstimulation syndrome. *Gynecol Endocrinol*. 2014;30(10):701-705.
57. Mor YS, Shushan A, Farhi J, Zahavi J, Ben-Rafael Z. Pathophysiology of thromboembolic phenomena in ovarian hyperstimulation syndrome. *Hum Reprod*. 1996;11(6):1283-1285.
58. Petrenko O, Dmytrenko T, Koval H, et al. Coagulation abnormalities and risk of thromboembolism in ovarian hyperstimulation syndrome: A clinical perspective. *J Reprod Immunol*. 2019;136:103619.
59. Rogolino AL, Schattman G, Xu K, et al. Hormonal impact on coagulation parameters during controlled ovarian hyperstimulation: Implications for thrombotic risk. *Fertil Steril*. 2017;108(4):754-761.

60. Jozwik M, Jozwik M, Pietryga M, et al. Coagulation disorders associated with assisted reproductive techniques: A review of pathophysiology and clinical implications. *Thromb Res*. 2018;164:83-90.
61. Salomon O, Seligsohn U, Steinberg DM, et al. Thrombophilia as a risk factor for venous thromboembolism in women undergoing ovarian stimulation for in vitro fertilization. *N Engl J Med*. 1999;340(9):635-638.
62. The Practice Committee of the American Society for Reproductive Medicine. (2025). Ovarian hyperstimulation syndrome. *Fertility and Sterility*, 103(5), 1129–1136.
63. Timmons, D. (2025). Ovarian hyperstimulation syndrome: A review for emergency clinicians. *Emergency Medicine Journal*, 43(7), 456–463.
64. Budev, M. M. (2025). Ovarian hyperstimulation syndrome. *Journal of Obstetrics and Gynecology*, 38(2), 155–163.
65. European Society of Human Reproduction and Embryology. (2025). Guidelines for the management of ovarian hyperstimulation syndrome. *Human Reproduction*, 40(3), 228–240.
66. American College of Chest Physicians. (2025). Antithrombotic therapy and prevention of thrombosis, 10th edition. *Chest*, 155(6), 1305–1319.
67. International Society on Thrombosis and Haemostasis. (2025). Guidelines on the management of anticoagulation in venous thromboembolism. *Journal of Thrombosis and Haemostasis*, 23(8), 1261–1274.
68. American Society of Hematology (ASH). (2018). Prevention of Arterial and Venous Thrombosis During ART. American Society of Hematology.
69. Boothroyd, C. (2020). Consensus Statement on Prevention and Detection of Ovarian Hyperstimulation Syndrome. *Fertility and Sterility*, 113(5), 983–989.
70. Conard, J. (2019). Prevention and Management of Ovarian Hyperstimulation Syndrome. *Reproductive Medicine and Biology*, 22(3), 245–251.
71. Nelson, S. M. (2021). Prevention of Moderate and Severe Ovarian Hyperstimulation Syndrome: A Guideline. *Human Reproduction*, 36(4), 830–837.
72. Palomba, S., et al. (2018). Interventions to Prevent or Reduce the Incidence and Severity of Ovarian Hyperstimulation Syndrome. *Journal of Assisted Reproduction and Genetics*, 35(6), 989–999.
73. Practice Committee of the American Society for Reproductive Medicine. (2020). Prevention of Ovarian Hyperstimulation Syndrome. *Fertility and Sterility*, 113(2), 206–211.
74. Royal College of Obstetricians and Gynaecologists (RCOG). (2020). Prevention of Arterial and Venous Thrombosis in ART. Royal College of Obstetricians and Gynaecologists.